RESEARCH DIGEST 1984–86

Alcoholism and Drug

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INTRODUCTION

The Research Digest is published biennially by the Addiction Research Foundation as a complement to its Annual Report.

As an agency of the Province of Ontario, the Foundation is charged by statute — The Alcoholism and Drug Addiction Research Foundation Act 1965 — with conducting programs of research, education, and treatment services. Although the Annual Report highlights some research achievements, the amount of information provided on each research program is necessarily limited.

The Research Digest is designed, therefore, to provide a general overview of the Foundation's current research programs and projects, and an update on recent progress. It is designed primarily for those who, though not necessarily researchers, have an interest in the Foundation's research initiatives. In this, the second issue, the Research Digest covers the two years from April 1984 to April 1986.

Foundation research is focused intramurally within the Social and Biological Studies and Clinical Institute divisions, which are located in Toronto, and in the London-based Community Programs Evaluation Centre of the Community Services Division. In addition, the Foundation supports the research activities of Professors Harold Kalant, Jat Khanna, Yedy Israel, Hector Orrego, and Larry Grupp in the Department of Pharmacology, Faculty of Medicine, University of Toronto; and of Dr. Peter Carlen at the Playfair Neuroscience Unit, Toronto Western Hospital. The majority of the Foundation's intramural investigators hold academic appointments in Ontario universities, primarily the University of Toronto.

The Foundation's research endeavors are wide in scope and have been designed to further the goals of the Foundation. Though relating specifically to Ontario, the Foundation's research has international relevance. Accordingly, the Foundation has been a World Health Organization (WHO) Collaborating Centre for research and training on alcohol and drug dependence problems since 1977, and in 1986 the ARF Biomedical Research Laboratory was designated a WHO Collaborating Centre for reference for cigarette smoke analysis.

Research descriptions prepared by program managers have been organized according to the divisional structure of the Foundation and, within these sections, by department and research group. The program of each research department has several research themes or lines, designed to contribute to the achievement of the Foundation's goals and objectives. Some lines are pursued within one department exclusively, while others are carried out in collaboration with other departments or institutions.

Each research theme or line is pursued through discrete research projects. Prior to their implementation, project proposals are subject to scientific peer review (including both external and internal reviewers), human ethics or animal care committee approval, and management approval. Descriptions of the research progress have been prepared by research department managers at the level of research lines.

Readers familiar with the Foundation's research over the years will note personnel changes in some key research management positions. Mr. Robert Popham and Dr. Wolfgang Schmidt have retired after long and productive careers as research leaders in the Foundation. Mr. Popham most recently held the position of director of the Social and Biological Studies Division, and Dr. Schmidt was head of the Social Policy Research Department. Dr. Howard Cappell has been appointed to succeed Mr. Popham as director, and social policy research has been amalgamated with program development research to form the Prevention Studies Department under Dr. Reginald Smart.

In the Clinical Institute, Dr. Edward M. Sellers has completed his term as division director and this position has been assumed by Mr. Edwin Watson. In addition, the behavioral and the health care systems departments have been integrated into a sociobehavioral research program under Dr. Adrian Wilkinson.

The 378 published reports which have emerged from the ARF research efforts during 1984–86 are listed at the end of this report.

Joan A. Marshman
President

SOCIAL AND BIOLOGICAL STUDIES DIVISION

The research of this division has as its principal goal the prevention of problems caused by the excessive or inappropriate use of alcohol and drugs. The achievement of this goal requires a base of knowledge from the biological, behavioral, and social sciences; only with such knowledge can attempts at amelioration and prevention of these problems be successful.

The work described in this section will be better understood and appreciated by those familiar with *Research Digest 1982–84*. Many of the specific programs and lines of research described there have continued. Although the division has been reorganized from three to two departments (Biobehavioral Research and Prevention Studies), most of the sections of these departments have continued, with established central themes drawn from the overall goals of the Foundation.

The research themes of the Prevention Studies program are diverse in content but united by the objective of producing practical knowledge with immediate applicability to the prevention of the alcohol and drug problems faced by Ontarians. The individual research programs take our scientists into schools, government, and law enforcement agencies concerned with traffic safety, workplaces, hospitals, and the community at large. Special attention is given to the implications for the health of the general public of regulatory measures and government policies related to alcohol and drugs, and to statistical trends in substance use and its attendant problems in the province.

In Biobehavioral Research, there are three main themes, all united by an interest in uncovering the mechanisms in the brain related to the following critical aspects of chronic use of alcohol and drugs: the acquisition, maintenance, and loss of this behavior; the tolerance and physical dependence associated with it; and the organic damage it often causes. The majority of this work is laboratory research conducted with animals.

The expertise of our scientists is applied to more than the pursuit of their own research. They contribute to the training of other professionals concerned with alcohol and drug problems, and they provide information and advice to individuals and institutions in Ontario and abroad. This is all done with the underlying conviction that the public response to alcohol and drug problems should be informed by the most accurate and up-to-date scientific information available.

Howard D. Cappell
Director, Social and Biological Studies Division

PREVENTION STUDIES
Program Manager: R.G. Smart

Research in prevention has as its ultimate purposes the understanding of alcohol and drug use and the eventual development of programs for the prevention of adverse consequences and the promotion of health among the people of Ontario.

This research involves: (a) epidemiological studies of the societal and psychosocial factors associated with alcohol and drug use; (b) the development and testing of primary and secondary prevention programs to reduce the incidence and prevalence of problems; (c) the evaluation of government measures affecting the availability of alcohol and drugs; and (d) policy analyses that focus on public health aims for alcohol and drug control measures and other preventive efforts.

There are eight major lines of research in the Prevention Studies research program:

1. Compilation of alcohol and drug statistics;
2. Adverse effects of alcohol use;
3. Extent of youthful drinking and drug use and the effects of legal controls;
4. Extent and consequences of the use of psychotropic drugs;
5. Research on drinking/driving practices and new programs for prevention of impaired driving;
6. Development and testing of educational programs for students and other high-risk groups;
7. Development of methods of preventing and treating alcohol and drug problems in employed populations;
8. Studies of the impact of regulatory measures on alcohol problems.

The first four lines involve surveys and special studies to discover the extent of alcohol and drug use and attendant problems and the factors associated with such problems. This work is related to the Foundation's need for a data-base for understanding the patterns of alcohol and drug use and resulting problems. However, it is also part of the knowledge base needed by governments and educational institutions to develop persuasive and regulatory measures with sound public health perspectives. Work on lines 5, 6, and 7 is concerned with the ARF objective of developing and evaluating superior programs to prevent and reduce drinking and drug-abuse problems in the Ontario population. The Prevention Studies research program pays special attention to the need for programs for drivers, workers, and school populations. The primary methods employed are comparison or quasi-experimental studies evaluating one type of program in comparison with another or with no program at all. The last research area involves studies of government regulatory or control efforts and policy analyses of the best government policy options in prevention.

1. Compilation and Analysis of Alcohol and Drug Statistics

The compilation of statistical data brings together readily available statistics on alcohol and other drug use and its consequences in Ontario, in Canada, and in other countries. The latest report in the series includes data up to 1984 on alcohol and other drug consumption and its medical, legal, social, and economic consequences.

The collection is continually being expanded, and material is being collected in print, microform, computer-printout, and machine-readable forms. Statistical documents, surveys, and studies are acquired from Statistics Canada, from federal, provincial, territorial, and municipal government agencies, and also from large market survey firms, marketing boards, and similar organizations in Canada. International statistics continue to be acquired from agencies such as the World Health Organization, the Food and Agriculture Organization, the United Nations, the Organization for Economic Co-operation and Development, and the European Economic Community, as well as from multigovernmental organizations, international marketing boards, and selected foreign governments such as the United States.

In addition to its function as a general reference work, this collection is used to prepare answers to requests for information received from researchers and government departments. It is also the source for statistical reports and research. Special compilations focus on specific target groups such as the young, the elderly, and women.

Statistical projects have been undertaken in conjunction with Health and Welfare Canada and representatives of other provincial governments in order to develop a National Drug Monitoring System and to prepare a report on Canadians and alcohol. A project undertaken in collaboration with the World Health Organization shows worldwide trends in alcohol production, trade, and consumption and in various aspects of alcohol- and drug-related problems. Liver cirrhosis deaths were linked to high alcohol consumption in over 50 countries, with the effect being more obvious several years after an upward trend in consumption has been recorded.

Other studies have focused on the areas of economics, social indicators, drug utilization, epidemiology, and health care management. The effects of economic well-being, affluence, and poverty on alcohol consumption were investigated. It was found that Ontario counties with high overall spending in retail sales also had high sales and consumption of alcoholic beverages. The changes in prices of domestic and imported alcoholic beverages were shown to have an impact on the choice of alcoholic beverages consumed. An analysis of the social costs of alcohol-related problems was undertaken; it included excess health care costs, value of reduced labor productivity, law enforcement costs, and social welfare costs. Recently, these were estimated at $1.6 billion for Ontario. Studies are currently in progress to update figures and to improve costing techniques.

Data on various aspects of alcohol and drug use were analysed in order to develop easy-to-use indicators of the burden imposed on society by alcohol and drug problems. This work

allows the easy identification of Ontario counties that exceed the provincial average or have particularly high levels of alcohol or drug problems, and it shows community workers how to identify specific high-risk target areas. Results are updated on a regular basis to take into account the latest available data.

A study of marketing sales data was undertaken to provide a detailed description of utilization of pharmaceutical drugs in Canada according to specific drugs and drug types. In the period 1977 to 1981, sales of analgesics and stimulants increased and sales of minor tranquillizers decreased for both drug stores and hospital pharmacies. There was also a steady substitution of acetaminophen products for ASA products as over-the-counter analgesics. Further detailed analyses are intended to identify shifts in use of psychoactive pharmaceuticals, including narcotic analgesics and minor tranquillizers such as the benzodiazepines.

A study of morbidity associated with high alcohol use was conducted using Canadian survey self-reports and Ontario medical records. High alcohol consumers had excess health problems including endocrine, nutritional, and metabolic diseases, mental disorders, diabetes, thyroid disorders, anemia, hypertension, bronchitis, emphysema, and ulcers. A study of alcohol-related problems in Ontario emergency departments showed that approximately 20% of all accident cases had an alcohol component. These studies help treatment personnel to identify specific morbid conditions in their alcohol patients and alert them to alcohol problems in their general patient caseload.

Investigator: M. Adrian

2. Adverse Effects of Alcohol Use

It has long been known from both clinical and epidemiological work that alcohol creates numerous adverse physical and social consequences. Excessive alcohol consumption leads to physical consequences such as liver cirrhosis, toxic reactions, and early death from a variety of complications. However, heavy alcohol use may also lead to social consequences such as drinking/driving, unemployment, domestic violence, and family break-up. A broad public health perspective requires the consideration of both the physical and social problems posed by alcohol. A variety of projects are examining these problems.

In Ontario, the level of alcohol consumption has been essentially stable for about 10 years — lately there has even been a small decline. The reasons for this stabilization (after a long period of increases) are being examined. They appear to relate to general changes in lifestyle, including increased attention to fitness and better nutrition, as well as changes in economic factors and availability of alcoholic beverages. Because of this relative decline in consumption, concomitant declines in rates of problems were expected. Data gathered so far indicate that problems such as liver cirrhosis have declined more than expected, but that not all problems have behaved in a similar fashion. Ongoing research is examining the extent of declines in problems and the reasons for them.

A large-scale project has been examining the effects of alcohol on lifespan. This type of study cannot be done experimentally with humans, and hence an animal model has been developed.

In a large colony of mice, mortality was studied in groups ingesting different amounts of alcohol and allowed to die at their own rates. Thus, through a study of experimental epidemiology it will be possible to determine whether or not the chronic consumption of specified doses of alcohol affects length of life in mice. The results of this study suggest that the life-limiting effects of alcohol occur at doses considerably higher than previously expected. However, the results are complex and must be carefully examined and replicated before firm conclusions can be reached.

A major review has explored the question: "Does moderate drinking prevent coronary heart disease?" A comprehensive study of epidemiological and laboratory research on the effect of drinking on mortality and morbidity from coronary heart disease and on possible mechanisms, particularly high-density lipoproteins, concluded that findings to date do not warrant changes in public education regarding the consumption of alcoholic beverages.

Two social issues that capture our attention virtually every day are unemployment and domestic violence. There are two separate projects being done, in cooperation with field consultants and professionals in the community, on how alcohol and drug abuse are involved in these phenomena. In the case of the unemployed, a sample of 400 males was taken from union lists. Interviews and questionnaires were administered to the unemployed individuals and their partners. Data are currently being analysed in relation to several hypotheses that predict drinking and drug-use behavior from pre-unemployment lifestyle factors. This analysis should throw some light on the dynamics by which problem drinking is precipitated or prevented in times of unemployment. Implications for interventions will then be sought through analysis and discussion with community professionals, union members, and other concerned parties.

The domestic violence study currently involves a large sample of battered women in shelters. Data are being gathered on how their own drug and alcohol use and that of their battering partners serve as responses to and as precipitants of aggression and violence. A further large-scale household survey is planned in order to determine both the prevalence of domestic violence in the population at large and the role of alcohol and drugs in it. Probably the dynamics of substance abuse is different in couples from which victims of violence end up in shelters, in comparison with the general population. At all events, it is important to understand these dynamics in order to develop ideas about effective preventive and remedial interventions.

Investigators: R. Ferrence, Y. Israel, R.E. Popham, W. Schmidt, M. Shain, R.G. Smart

3. Extent of Youthful Drinking and Drug Use and the Effects of Legal Controls

Illicit drug use among adolescents and young adults continues to be an important problem. Most illicit drug use involves young people; they are also a group in which drinking and drinking/driving problems have increased greatly over the past generation. They represent an important focus for society as a whole and especially for policymakers interested in drug abuse. Consequently their illicit drug use is being examined in several research projects. Research is directed to monitoring and understanding the trends in drug abuse and the effectiveness of legal controls with a view to improving them. The hope is to

provide information that will lead to better policies for the prevention and control of drug abuse by young people. The major drugs of concern for young people are alcohol, tobacco, cannabis, and lately cocaine.

Trends in drug use and abuse require careful monitoring. Since 1977 a large-scale biennial study has been made among Ontario students. The last data, collected in 1985, showed an unprecedented decline in drug use. In fact, reported use of 8 of the 17 drugs declined significantly (including tobacco, glue, other solvents, medically prescribed barbiturates and tranquillizers, and stimulants). Also, use of most other drugs declined by small amounts. Only the use of cocaine showed no change, with the exception of an increase in reported use in Metro Toronto. These changes appear to be associated with declines in the availability of cannabis and increased concern about the health and moral aspects of drug use. Unfortunately, heavy or daily use of alcohol and cannabis did not decline. Special studies have been made of how religious affiliation and participation protect against drug use. Also, analyses of ethnic status and drug use are planned. It is expected that the school survey will be repeated in 1987.

The methods used in the survey of Ontario students have been the basis for a set of guidelines for such surveys published by Health and Welfare Canada as "Guidelines for the Development of Canadian Surveys of Alcohol and Drug Use among Students."

Cannabis is still the most commonly used illicit drug, although the frequency of use appears to be decreasing. The criminal law that makes its possession and sale illegal under the Narcotic Control Act continues to generate a substantial number of convictions — nearly 25,000 in 1985. A fine, rather than discharge, remains the most common outcome in Canada for a charge of simple possession. Young persons aged 15–19 years account for more than one-fourth of all cannabis-related convictions nationally, and they do *not* receive markedly more lenient sentences than older offenders. Interviews with those criminalized for cannabis possession revealed a general ignorance of drug law even after firsthand exposure to the courts, a fatalism about the sentences conferred, and a basic rejection of the cannabis law.

Other work has documented the emphasis in the 1980s on health concerns regarding cannabis; these have tended to supersede the legal issues that took precedence in the debates of the 1970s. A study of adult cannabis users in the community was conducted to learn how they learn to live with the legal prohibition while maintaining their practice of regular use. For this group, health concerns rather than legal ones appeared to moderate their intake. These adult users often expressed support for existing controls in the interests of protecting the younger members of the population. Hopefully this research will help the development of preventive strategies that will minimize the hazards of cannabis use at an acceptable level of social cost.

Cocaine has been a relatively recent arrival among popular illicit drugs in North America. Despite cocaine use levels in Canada that are considerably lower than those documented in the United States, the potential harmful effects are serious enough to warrant concern. The main purpose of a study of 111 social-recreational users of cocaine in the community was to learn how this drug was being used and obtained and how it was affecting those who were "typical" users rather than extreme cases requiring treatment. The appeal of cocaine, according to users, was a combination of its status as a glamor drug, its euphoric effects, and users' sense of remaining in control. Most used cocaine socially, acquired it from friends, and generally separated it from work activities. Reactions to cocaine included some episodes of violence and paranoia and, for some users, a craving for more cocaine; the occurrence of these reactions, and of other relatively less serious effects, was related to frequency of cocaine use. Clearly, there was a broad variety of experience with cocaine, ranging from infrequent use that appeared to pose no problem or social difficulties to compulsive use that posed a host of health and other personal problems. The law against cocaine was regarded by virtually all respondents in this study as a remote and largely irrelevant threat. Other aspects of cocaine that were covered in this project included the history of its use and legal repression in Canada, the image of cocaine in popular culture, a review of the world literature on trends in cocaine use, and an overview of enforcement and sentencing trends in Canada. This work aims to place the concerns over cocaine in an informed context and replace some of the extreme characterizations of cocaine — both favorable and negative — found in popularized accounts.

Another study examines the meaning and nature of drug "dependence" or "addiction" and the ways in which different conceptualizations of the phenomenon have had impact on social responses to it. This research examines the socio-historical processes that shape definitions of drug dependence, the factors that impede the development of dependence in users, and the complex interactions among epidemiological changes, public policy positions, and therapeutic responses.

Since drug abuse is a worldwide concern, some epidemiological studies have an international focus. Much work is done in collaboration with the World Health Organization (WHO), as the Addiction Research Foundation is a WHO Collaborating Centre. An international review of the epidemiology of cocaine use and abuse has been developed for a WHO Working Group on Cocaine and Coca Paste Abuse. Also, a review of epidemiology and prevention programs for solvents has been made for a WHO Advisory Group on Solvents and Other Volatile Substances, meeting in 1986.

Investigators: J. Blackwell, P.Erickson, M. Goodstadt, R.G. Smart

4. Extent and Consequences of the Use of Psychotropic Drugs

The purposes of research in this area are to monitor trends in consumption patterns of psychotropic drugs in Canada and to study factors associated with heavy consumption. These drugs are chiefly those obtained on prescription and those having significant mood-modifying effects. However, some research on tobacco smoking has also been done.

Psychotropic drug use is being studied in a variety of ways. Arrangements have been made to obtain data on psychotropic prescribing patterns in Ontario. Plans are also being made for a review of the most recent trends in psychotropic drug use and its problems in Canada. Use is monitored by means of a regularly occurring survey of adults. Approximately 1,000 persons aged

18 and over in a household sample are interviewed about every two years concerning their alcohol and drug use. In 1984, as in the past, the most commonly used drugs were tranquillizers, followed by sleeping pills and stimulants. No increase in use was found in 1984 as compared to 1982. Both tranquillizer and sleeping-pill use was more common among females than males and among middle-aged or older persons than younger persons. Heavy daily tranquillizer and sleeping-pill use seems most common among the elderly. Hence a special study is being made of the rates of drug use among the elderly and how they have changed since the surveys began in 1976.

Exploratory research has been conducted into the non-medical drug use of psychiatric patients. A sample of crisis admissions were interviewed to obtain self-reports of the impact of drug use on mental health, including the occurrence of adverse psychological drug reactions. Research also focused on the use of drugs to self-medicate psychiatric symptomatology. Both of these factors appear to be important in influencing consumption patterns in this psychologically vulnerable population. On the basis of this experience, a larger and more systematic study is under way to explore the relationships between drug use and schizophrenia, affective disorders, and other mental illnesses.

One ongoing project is investigating the role of social and economic factors in patterns of cigarette smoking in Canada. This provides an alternative perspective to most investigations of smoking behavior, which are based on psychological or physiological models. The study uses a diffusion model to explain temporal variations in smoking by sex, age, region, and social class. Diffusion theory suggests that the adoption of new behaviors is best described by an S-shaped curve, similar to that which describes epidemics, and that "early adopters" have higher social status, greater access to sources of communication, and many other characteristics that differentiate them from "late adopters." Data from the Canada Health Survey were used to reconstruct sex-birth cohorts and to estimate rates of smoking for various social and demographic categories. Results to date indicate that the diffusion model explains much of the variation in rates of smoking and can suggest new approaches for prevention.

Investigators: J. Blackwell, R. Ferrence, R.G. Smart

5. Research on Drinking/Driving Practices and New Programs for Preventing Impaired Driving

Drinking and driving is a complex and persistent problem. Drinking/driving accidents are a significant cause of death in Ontario, especially among young persons. About half of all drivers killed in accidents have been drinking. However, in the last two to three years there has been some evidence that alcohol-related fatalities have been decreasing in Ontario. Although it is not yet possible to isolate the reasons for this decline, the purpose of the Foundation's drinking/driving research is to contribute to the knowledge base needed to reduce the prevalence of alcohol-related crashes. Our work is focused on the three modes of prevention: primary (education), secondary (legal controls, enforcement, and adjudication), and tertiary (rehabilitation).

Primary prevention has often been viewed as the preferred means to reduce the drinking/driving problem. One such strategy that has received increasing attention in recent years is the implementation of programs in the schools to prevent impaired driving. A comprehensive review of these programs has provided some important observations. For example, it appears that the context in which these programs are administered may be an important determinant of their effectiveness, as is the style of their presentation. As yet, the impact of individual programs on traffic safety has not been assessed, but it appears that well-designed programs have a positive impact on knowledge, attitudes, and possibly behavior. Another primary prevention strategy is to identify individuals at high risk for crash involvement, so as to permit the application of special measures to reduce that risk. Research studies are planned and under way that will examine the relationships between several individual and environmental factors and likelihood of alcohol- and drug-involved accidents. The resulting information will be of great importance in identifying high-risk groups and in developing intervention programs.

Every component of secondary prevention — the legal system — is being studied in order to understand the strengths, successes, and problems in the system. The impact of new drinking/driving laws has historically been mixed. Very little research, however, has been done to assess which components were necessary to maximize the potential for success. The evaluation of the 12-hour licence suspension law was designed for this purpose. Immediately after the introduction in Ontario of the new law, there was a significant decrease in drinking/driving fatalities in Ontario compared to Saskatchewan and Manitoba. However, this reduction lasted only two months. A reasonable hypothesis was that laws could only be effective if the public knew about them and they were being enforced. Unfortunately, such was not the case. Lack of an organized long-term education campaign prevented the Ontario public from having much knowledge about the new law, and many Ontario police forces' lack of roadside screening devices precluded their being able to enforce it. This evaluation, then, demonstrated the importance of education and enforcement for legal controls in the deterrence process. A collaborative project is under way with the Ontario Provincial Police on the 12-hour law. The London detachment of the OPP has been involved in a high-profile, intensive spot-check program. The data from this program should offer an interesting comparison for the Ontario-wide data.

The adjudication and sanctioning of drinking/driving are being studied through a survey of Crown Attorneys in Ontario. In collaboration with the Ministry of Attorney General, Criminal Law Division, and the Crown Attorney Association, data have been gathered, and we hope that useful information will be obtained on ways to maximize deterrence through the legal system.

An important tertiary prevention study is now being conducted. In the early 1970s the Foundation sponsored two rehabilitation programs for drivers convicted of a second drinking/driving offence. People who participated in these programs are now being interviewed about their driving habits, drinking habits, and other health-related behavior. These data will be combined with data gathered at the time the program occurred, and will include driving record data. The study will

provide important information about the long-term effects of such programs, about factors that predict success or failure in such programs, and about the general prognostic value of a second conviction for impaired driving. The other major rehabilitation study, which will also have implications for primary and secondary prevention, is a collaborative venture with the Trauma Unit of Sunnybrook Medical Centre. There are three parts to this study, and it is expected that the results will answer the following questions: (1) Does a positive blood level increase the severity of injury and hinder the recovery of trauma victims? (2) What are the differences, if any, in characteristics between accident-involved drinking drivers and non-drinking drivers and culpable (i.e., responsible for the accident) and non-culpable drivers? (3) How are trauma victims faring one year after the accident? Information from this study will be invaluable both for the treatment of trauma victims and for the development of accident prevention strategies.

Investigators: R. Mann, E. Vingilis

6. Development and Testing of Educational Programs for Students and Other High-Risk Groups

Young people have continued to be the focus of most of the educational research effort in the past two years. The reasons for this priority derive from the common experience of parents, teachers, and young people themselves. There is also a large body of research that supports the special concern for the needs and problems of children and young adults during their formative years. With respect to drug use in particular, it has been found that the earlier young people start using drugs (including alcohol, tobacco, and illicit drugs), the more likely they are to encounter problems through their use. Analyses of our surveys of Ontario students have also provided evidence that the most rapid increase in drug use occurs between grades 7 and 9, peaking in grade 11.

Recent research has continued to examine the impact of alternative approaches to cannabis education. These experimental programs compared the value of concentrating on the health consequences of cannabis use vs. the legal risks of use. This research has demonstrated that a program that incorporates a consideration of *both* health and legal risks is most effective in producing desirable changes in attitudes toward cannabis use, which, in turn, are related to a reduction in intentions to use the drug in the future. Of special importance is the consistent finding that a program that concentrates on the potential legal consequences of cannabis use fails to have any desirable effect; this finding is in agreement with the generally poor performance of other legal-deterrence efforts.

It has long been felt that most programs are aimed at, and are probably only effective for, the average (non-abusing) student. For a number of years an effort has been made to develop an educational intervention that has an impact on young people who are at higher-than-average risk for drug use (i.e., those who are already experiencing problems or are likely to develop problems in the near future). Undertaken in conjunction with the Ontario Ministry of Community and Social Services, a new program has been designed to enhance much-needed self-management skills in this group. It has been tested with a variety of "high-risk" youth — those who have been found guilty of various criminal offences and are currently in custody or on probation. Preliminary results have been encouraging, in that the self-management program appears to have had a positive impact on the young offenders and has been well received by both recipients and staff. The next challenge is to render the program more permanently effective. Plans have been developed to extend the program's implementation to include the young offender's parents (or other significant adults). This next stage is being undertaken in collaboration with staff from the Ministry of Community and Social Services and from the Foundation's Community Services and Clinical Institute divisions.

The importance of this work is twofold. Firstly, there is growing concern among those responsible for young offenders that their number, and the nature of the problems with which they are faced, will increase as a result of the changes from the former Juvenile Delinquents Act to the new Young Offenders Act. Secondly, there is, in addition to the young offenders, a very large number of young people who are for other reasons at risk with respect to their current or future drug use. An effective program for these young people would make a major contribution to solving an important social problem.

Previous research (conducted in 1981) showed that more than 50% of Ontario school boards offered no drug-related material in any curriculum area. However, many of these boards were planning to develop such material. A new and more extensive survey of all the Ontario school boards has therefore been undertaken to determine the current level of drug education programming, the drug education resources available throughout the province, and school administrators' perceived needs in this area.

In the most recent (1985) Ontario student survey, the majority of students reported receiving no drug education; where they did receive some, it was limited to only one or two classes in the year. These findings suggest a fundamental question: "What is really happening in the Ontario classrooms with respect to drug education?" It is known that many informal opportunities for drug education arise within the course of a school year, in addition to the more structured opportunities in drug education curricula. A new project examines how much drug education actually occurs in the classroom.

ARF staff have evaluated the implementation of a new drug curriculum developed by an Ontario board for primary grades. This research has involved in-depth interviews to determine the levels of curriculum use by teachers and their level of concern about the curriculum. It should provide more accurate information concerning the nature and extent of drug education within typical Ontario classrooms. Other aspects will permit the evaluation of the impact of alternative modes of teacher training on the implementation of the program. It will, in addition, examine the program's effectiveness on an unusually young audience (grades 2–3). Future phases of the research will include the extension of the curriculum through the junior, intermediate, and senior grades.

A totally new medium of drug education has been explored during the past two years. Work has begun with one of the major suppliers of television to patients in Ontario hospitals.

Initial analysis indicates that hospital patients are receptive to health/medical programs transmitted through this medium. Present plans involve the "broadcasting" of drug-related programs to appropriate audiences (e.g., on tobacco use to young mothers in the obstetrics/gynecology wards; on prescription and over-the-counter drug use to the elderly). Evaluation of such an approach to drug education is expected to result in the identification of a new means of reaching highly relevant target groups in a way, and in a setting, that is potentially very cost-effective.

Investigator: M. Goodstadt

7. Development of Methods of Preventing and Treating Alcohol and Drug Problems in Employed Populations

An earlier view of alcoholics was that they were primarily skid row residents or chronic inebriates. It is now recognized that alcohol and drug problems occur at all social-class levels. In fact, most people with alcohol and drug problems are employed, and for this reason the Foundation pioneered a number of Employee Assistance Programs (EAPs). The underlying rationale for them is that, with the help of employers, alcoholics and drug abusers should be identified and treated at an early stage in their drinking or drug use careers. Most EAPs involve specific policies allowing identified alcoholics and drug abusers to maintain their jobs, without further disciplinary action, provided they seek treatment. Many forms of EAPs have been made available to the workers of Ontario. It is essential that we test a wide variety of EAPs for their effectiveness.

The workplace now harbors a wide variety of interventions that are known or believed to have remedial or preventive impact upon alcohol and drug abuse. Prominent among these interventions are the older EAPSs and the newer Health Promotion Programs (HPPs). In a just-published book called *Healthier Workers* the impact of these strategies has been reviewed and criticized by ARF research staff, who conclude that workplace programming tends to be directed toward either the "walking wounded" (those whose problems are advanced) or the "conspicuously well" (those who would be well with or without external help). These initiatives (EAPs and HPPs) are rarely coordinated with each other or with Health and Safety or Quality of Working Life programs.

Taken as a whole, industrial programs tend to be fragmented and thus less effective than they could be. Further, they tend to miss altogether those employees who form the majority of the workforce, those we might refer to as the "moderate-risk group." These are the people who are experiencing mental and physical health problems that if not resolved will probably get worse, making them candidates for EAPs. A last category includes people in states of chronically mediocre health who could be feeling and performing much better. All these conditions may be in one way or another associated with lifestyles in which excessive alcohol and inappropriate drug use feature. The apparently low-grade problems that these groups manifest nonetheless represent a net loss of considerable proportions to their employers in terms of lost productivity, sickness and absenteeism rates, and low morale.

A comprehensive approach to the needs and risks of the *whole* workforce is required, which embraces the full spectrum of preventive and remedial programs. A theoretical model of such an approach has been developed and termed the Employee Health and Assistance Program (EHAP). This model is elaborated in *Healthier Workers*. Currently, researchers and program consultants at ARF are engaged with the Health Promotion Directorate of Health and Welfare Canada in an exciting new research project that will test the efficacy of this prototype in selected sites in Ontario. The key to the project is "process": involvement of workers themselves in the design and execution of interventions for which they have indicated a need. The research objective is to measure the degree to which such an approach allows us to identify specific health needs and risk clusters in ways that suggest programmatic or even structural interventions. It is anticipated, too, that it will be more cost-efficient and effective to run EAPs and HPPs in synergistic harness as an Employee Health and Assistance Program.

Investigator: M. Shain

8. Studies of the Impact of Regulatory Measures on Alcohol Problems

A longstanding and highly productive line of research has assessed the impact of regulatory measures on the frequency of various alcohol-related health and social problems. The early work focused on the distribution of alcohol consumption. The main practical conclusion drawn from this research was that any measure that affects the overall level of alcohol consumption in a population is likely to affect the prevalence of alcohol problems. It has led to a variety of studies of government regulatory measures such as those concerning advertising of alcoholic beverages, "happy hours", and the possibilities and problems of introducing wine into grocery stores in Ontario. Also, a major study of drinking in taverns and bars is under way, as well as a study of how heavy drinking may be modified with public health measures.

Since changes in overall alcohol consumption should be accompanied by similar changes in the prevalence of heavy drinkers, an important principle of prevention is established. The number of heavy drinkers probably cannot be reduced without an accompanying reduction in the overall consumption level of a population. The Ontario Prevention Study was designed to test this hypothesis. In 1984, a survey of alcohol consumption was conducted and numbers of heavy drinkers were identified in two Ontario communities. The experimental community was subjected to various intervention techniques aimed at raising its level of awareness of alcohol problems and reducing the consumption of heavier drinkers. A follow-up survey conducted in 1986 in the experimental and control communities will reveal the impact of changes in the consumption behavior of heavy users on the distribution of consumption in the community at large. It will also give information on the value of indirect methods of estimating the prevalence of hazardous consumption and on the effectiveness of secondary prevention programs.

One immediate outcome of this line of research was the symposium in 1985 entitled "The Application of Research on Developing Community Action Against Alcohol Problems." The symposium offered a unique opportunity for researchers,

program developers, and community planners to exchange views on how to facilitate effective prevention of alcohol problems at the community rather than the national level. The proceedings of this symposium are being published by the Foundation under the title *Prevention, Alcohol and the Environment — Issues, Constituencies and Strategies*.

Currently a study of drinking behavior in licensed establishments is focusing on the nature of the drinking environments, rates of drinking, and socio-demographic correlates of drinking behavior. The study examines situational determinants of heavy drinking and drinking problems and how regulatory mechanisms can affect drinking behavior and prevent problems. This research has produced two notable products over the past year. First, in connection with the public drinking study, a major symposium was organized in collaboration with provincial licensing officials and the federal government. The meeting brought together scientists engaged in tavern studies with representatives of eight provincial licensing boards in a unique and productive dialogue between policymakers and researchers. The proceedings of this symposium were published by the Foundation in 1985 under the title *Public Drinking and Public Policy*. Second, the preliminary results of the study have been utilized in the development of a server intervention program in collaboration with the Foundation's Community Services Division. Entitled *A Guide to the Responsible Service of Alcohol*, the program consists of a videotaped presentation plus three manuals — one for servers, one for managers, and one for trainers. It presents a wealth of information about the obligations and civil liabilities of licensed establishments, alcohol and its effects, how to recognize intoxication and prevent it, and how to manage an intoxicated person. Its purpose is to establish serving practices and management policies that prevent habitual heavy drinking, drinking to intoxication, and impaired driving.

Several studies of how alcohol advertising affects drinking have been made. These include econometric studies and assessments of the impact of advertising bans. More recent have been experimental studies of the effects of television advertising. In general, the research indicates that alcohol advertising has little impact on overall consumption in the population or on the drinking of people in the experimental studies. An experimental study of the effects of beer commercials on the drinking of young males showed little impact. A new study, involving young women who watched alcohol commercials on television and at the same time could drink wine in a social situation, is currently being made. Further study in this complex area is certainly needed to determine the impact of advertising on drinking.

Another area for research has been "happy hours," which were introduced into Ontario a few years ago. A survey of drinking establishments in Toronto found that about 25% had a happy hour. There was a very wide variety of happy hours: some involved two-for-one discounts; other featured reduced prices; as well, the length of the "hour" varied greatly. Because of the limited nature of many happy hours, and because a minority of licensed establishments had them, they should have had a limited effect on overall consumption of alcohol. When happy hours were recently banned, possible reductions in overall consumption in Toronto, drinking/driving, and the consumption in bars were studied.

An important concern in Ontario has been around the possible introduction of beer and wine into grocery stores. A detailed policy analysis of the probable effects of such an introduction was made. It examined experiences from other jurisdictions, statistical data on the probable increase in sales in Ontario, and a wide variety of data on the prevention of problems. This analysis concluded that beer and wine in Ontario grocery stores would likely increase both overall consumption and problems from alcoholic beverages. It was therefore argued that, on the basis of public health concerns, their availability in grocery stores is inadvisable. The results of this policy analysis have been made widely available to policymakers and interested community groups in Ontario.

Investigators: N. Giesbrecht, P.M. Kohn, E. Single, R.G. Smart

BIOBEHAVIORAL RESEARCH
Program Manager: H. Kalant

Research in this department during 1984–86 has been directed toward providing answers to three major theoretical questions and a subsidiary methodological problem:

1. What features of the action of alcohol and other psychoactive drugs on the nervous system cause an individual to acquire, maintain, and increase the practice of drug-seeking and drug self-administration?
2. What behavioral, physiological, and neurochemical mechanisms give rise to the development of tolerance to and physical dependence on alcohol and other drugs, and how do these factors interact to control the rate and extent of tolerance development?
3. What types of organic damage are produced by chronic heavy ingestion of alcohol, cannabis, and other drugs, how is such damage produced, and what factors affect its production and severity?
4. Several of the studies to be described below have required the analysis of minute amounts of drugs or of chemical transmitter substances in the brain and blood of laboratory animals. The fourth research area has been the development of new microanalytical methods for use in these studies.

All of this work is related to the Foundation's responsibility to increase knowledge of the biological and sociobehavioral determinants of the acquisition and control of drug- and alcohol-consuming behavior, and of the basic mechanisms and significance of tolerance and dependence. The first focus mentioned above is also related to the Foundation's goal of developing and testing possible pharmacotherapeutic agents for the treatment of those with alcohol-related problems, and the third focus bears directly on the Foundation's aim to increase knowledge needed for developing methods of preventing or ameliorating chronic physical and behavioral adverse consequences of the use of cannabis and other drugs.

1. Studies of Factors Governing Self-Administration of Alcohol

It is generally accepted that drugs with addictive liability act upon a specific set of structures or pathways in the brain to produce effects ("reinforcement") that increase the probability of future self-administration of the drugs. Identification of this reinforcement system, and elucidation of the nature of its interaction with addictive drugs, is perhaps the most fundamental biological research question in the field of addiction studies. Work during the past two years has included a number of different approaches to the study of reinforcement by ethanol. So far, there is no adequate theoretical model to orient research into brain mechanisms of reinforcement by ethanol, and no convincing animal model of alcoholism comparable to the intravenous self-administration model for cocaine and opiates (see below). Therefore, much of the work described in this section is, of necessity, exploratory methodological research aimed at developing reproducible high-dose voluntary intake of ethanol in the rat. When this methodology is achieved, it will then be possible to study the neural mechanisms involved and to test potential therapeutic interventions.

The Meisch technique consists in training partially food-deprived rats to press levers to obtain access to drinking spouts that provide fixed quantities of alcohol solution and of water. Previously, we have found it possible with this technique to induce normal rats to ingest regularly amounts of ethanol (even as a 32% solution) in excess of 10 g/kg daily, despite equal availability of water, and to produce high blood alcohol levels (BALs) and tolerance. This work has now been repeated with genetically selected alcohol-preferring (AA) and non-preferring (ANA) rats from the Alko Laboratories in Finland. Both groups acquired alcohol-drinking behavior in this model, but the AA rats started at higher levels than the ANA, and rapidly progressed to intakes of up to 14 g/kg daily, with BALs of up to 240 mg/dL and clear tolerance. The ANA never went beyond daily intakes of 6 g/kg, had BALs ranging from 0–109 mg/dL, and did not acquire tolerance. The results indicate a clear genetic influence on acceptance of alcohol.

However, a drawback of this model is the need for food restriction as a motivating factor in learning to bar-press for alcohol. Other models have therefore been tested. Rats that were neither food- nor water-deprived were found to drink sufficient alcohol to produce BALs of 50–130 mg/dL when offered alcohol for one hour a day in a special drinking cage. Genetic and physiological factors are suggested by the observation that Wistar rats drank more than Sprague-Dawleys in this model, and had slower absorption of alcohol from the gastrointestinal tract. These animals are clearly not alcohol-dependent, but the factors controlling their intake may be relevant to the question of transition from normal to excessive drinking.

Further evidence of the role of genetic factors in the control of ethanol intake has come from a comparison of five different strains of rats differing in their initial sensitivity to the intoxicating effects of alcohol. Groups of Wistar, Sprague-Dawley, Long-Evans, Holtzman, and Fischer-344 rats were tested for their sensitivity on the hypothermia and tilting-plane (motor coordination) tests, and for alcohol intake in two different paradigms: (a) voluntary intake of 5% (v/v) ethanol and water in a 24-hour two-bottle free-choice test; (b) presentation of ethanol (5, 10, or 20% v/v) and water separately, on alternate days. There was no apparent relationship between alcohol sensitivity and intake, and it is possible that under these conditions the intake is controlled by the smell, taste, or other peripheral sensory effects of alcohol rather than by its central intoxicating effects. Since these sensory responses to alcohol are also under genetic control, the genetic-strain differences in ethanol intake may reflect various genetic controls, and not exclusively that relating to reinforcing effect.

The Meisch technique, mentioned above, involves a complex training procedure in which partially food-deprived rats first learn to press a lever to obtain water when a small amount of food is present in the operant box. Then the water is replaced by progressively stronger alcohol solutions, and finally food is no

longer placed inside the box during the drinking sessions. A series of experiments was carried out to assess the importance of each of the following factors: (1) the initial body weight reduction (food restriction), (2) the presence of available food inside the box during training, (3) the type of food placed in the box, (4) gradual progression of alcohol concentration, and (5) production of thirst by water deprivation in the home cage rather than by presentation of dry food. The relative importance of these factors proved to be 1 > 2 > 4 > 3 and 5. These findings do not answer the question of whether food restriction increases the intake of ethanol because of the calories it provides, or because of some non-specific effect of hunger on general activity (including drinking), or because alcohol (and many other drugs) may reduce the perceived level of hunger. However, they emphasize the importance of trying to develop a procedure that results in sustained high levels of intake, but without recourse to food restriction.

In earlier work we had observed that factors that increased the activity of the renin-angiotensin system (a physiological mechanism for conserving salt and water in the body and maintaining blood pressure) inversely affected voluntary alcohol intake; that is, increased angiotensin levels decreased alcohol intake, and decreased angiotensin caused increased alcohol intake. This relationship has now been confirmed via the Goldblatt renal hypertension model: a clip applied to one renal artery, to reduce blood flow to that kidney, increases the circulating angiotensin levels, produces hypertension, and reduces alcohol intake in both the 24-hour two-bottle free-choice test of alcohol vs. water and the 1-hour-daily limited-access test of alcohol intake. However, neither continuous infusion of angiotensin by subcutaneously implanted osmotic minipumps, nor direct injection of angiotensin into brain regions known to contain angiotensin receptors, affected alcohol intake by rats trained by the Meisch procedure. In contrast, destruction of the area postrema, a site rich in angiotensin receptors that is located outside the blood-brain barrier but communicates by nerve-fibre tracts with various brain sites, more than doubled the alcohol intake. It is possible that the doses of angiotensin used in the preceding experiments were inappropriate; this is being explored in further studies.

Investigators: L.A. Grupp, H. Kalant, J.M. Khanna, M.A. Linseman, A. Stiglick

2. Studies of Self-Administration and Motivating Properties of Opioids

Various methods used in this laboratory permit inferences to be made about the positive ("reinforcing") and negative ("aversive") motivating properties of morphine-like drugs. One of these involves a simple test in which rats are trained to run down a straight runway to receive a saccharin-sweetened food reward and an injection of either morphine or saline. On subsequent tests, the rats that had received morphine ran more rapidly (an indication of reinforcing effects) but ate less saccharin-sweetened food in the goal-box (an indication of conditioned taste aversion caused by the morphine). This result confirms, within the same paradigm, earlier findings by other investigators who had shown reinforcing and aversive properties of morphine in separate paradigms.

This method has been used to test a widely discussed current hypothesis that reinforcement by opiates results from an action of the drugs on dopamine neurons in the ventral tegmental area (VTA) of the midbrain. The hypothesis was tested by injecting morphine directly into this area, via an implanted cannula guide, when the rats ran down the runway to the goal-box. Surprisingly, on subsequent tests the rats did *not* run faster (i.e., no evidence of reinforcement was seen), but they did show taste aversion to saccharin-sweetened food that had been paired with the morphine injection. Similar findings were obtained when morphine was injected into the cerebral ventricle instead of the VTA. In another runway experiment, pretreatment with systemic methylnaltrexone (an opiate receptor blocker that does not pass readily from the blood into the brain) prevented the increase in running speed that normally followed administration of morphine in the goal-box, but did not prevent the conditioned taste aversion to saccharin. These findings suggested that runway speed may be determined at least in part by peripheral actions of morphine rather than by a central reinforcement mechanism, while the taste aversion effects are exerted within the brain.

The problem is further complicated by the fact that at least four different types of opiate receptors are known, designated as "mu," "kappa," "sigma," and "delta" (and possibly a fifth or "epsilon" type), which mediate different actions of opioid drugs. During the past year, we have started a systematic examination to map the motivational effects of activating these various receptors separately by studying the consequences of different receptor-specific drugs on conditioned taste preferences and place preferences (see *Research Digest 1982–84* for an explanation of the place preference test). So far, only selective "mu" receptor agonists have produced conditioned preferences indicative of reinforcing properties; "kappa" and "sigma" agonists appear to be either motivationally neutral or aversive. Naloxone, a selective "mu" blocker, has detectable aversive properties that are decreased by lesions of the arcuate nucleus of the hypothalamus, which contains the cell bodies of brain cells producing the endogenous opioid peptide, β-endorphin. These findings suggest that the β-endorphin neurons may be involved in the reinforcing effects of food, water, and other natural reinforcers. This possibility is being explored further.

Another type of motivating effect, designated as negative reinforcement, is postulated to occur when an opiate drug is used to relieve aversive withdrawal symptoms in a physically dependent subject. The aversiveness of the withdrawal reaction has been demonstrated by the occurrence of a conditioned aversion to a specific environment in which rats or mice, previously made physically dependent by subcutaneous implantation of morphine pellets, have experienced a withdrawal reaction provoked by systemic or intracerebral injection of naloxone. This work is continuing.

A major effort has been devoted to the study of reinforcement of opiate self-administration in an operant behavior model. Rats are trained to press a lever to deliver an intravenous infusion of heroin via an indwelling catheter. Extensive preparative work has culminated in the development of a laboratory with sixteen operant chambers linked to a microcomputer that both controls the experiments and records and analyses the results. By appropriate selection of

limited-access conditions and low dosage of heroin, it has been possible to show rapid acquisition of heroin self-administration without physical dependence, so that the direct positive reinforcing effects of heroin can be studied without the confounding factor of negative reinforcement.

This procedure has now been applied to a mapping of possible sites in the brain at which opiates may exert the actions that produce reinforcement. Methylnaltrexone (see above), if injected into a specific brain site, does not diffuse away from that site very readily, and therefore a very small dose can be given there to produce a localized action. Rats trained to self-administer heroin intravenously have been given local injections of methylnaltrexone at various sites, to test its ability to block heroin reinforcement. To date, three brain sites in addition to the VTA have given positive results; further mapping is continuing. The same sites are also being tested for their role in re-initiation of drug self-administration. A rat that has been trained to bar-press for heroin, but then has had this behavior extinguished, will rapidly re-establish it when given a small intravenous "priming" dose of heroin. The brain sites at which methylnaltrexone can modify heroin self-administration behavior are also being tested for the ability of priming injections of opiates at those sites to re-initiate the behavior. The results will not only provide basic knowledge about the brain mechanisms involved in drug abuse and dependence, but may also have implications for future development of pharmacological interventions for treatment.

Finally, self-administration of small doses of heroin has been observed to be accompanied by increased arousal and locomotor activity, which are thought to be the rat's equivalent of euphoriant effects in humans. Injection of methylnaltrexone into the cerebral ventricles appears to reduce the arousal effects and the self-administration behavior in parallel. A study of the effects of injection into the brain tissue itself is now in progress, to assess whether the sites at which methylnaltrexone blocks heroin self-administration are the same as those at which it blocks heroin-induced locomotor activity.

Investigators: W.A. Corrigall, T. Hunt, R.F. Mucha

3. Studies on Mechanisms of Tolerance to, and Cross-Tolerance between, Alcohol and Other Drugs

Many different aspects of the development of tolerance have been examined during the past two years as part of a long-continuing program of research into the basic adaptive changes in the nervous system resulting from chronic exposure to alcohol and other drugs. The different approaches correspond, to a considerable extent, to the different levels of analysis — subcellular, cellular, integrated nervous system, and whole organism — at which the phenomenon can be studied, and to the techniques appropriate to each level.

One of the unanswered basic questions about tolerance is whether individual and species differences in sensitivity to a drug on the first exposure ("initial sensitivity"), in acute tolerance (i.e., increased resistance developing during the course of a single exposure to the drug), and in chronic tolerance (developing during repeated exposure) are all related to the same brain mechanisms and influenced by the same factors. This question has been studied by two different approaches: (1) Large numbers of Wistar rats and of Swiss Webster mice were tested for their initial sensitivity to the effects of ethanol on body temperature and motor coordination, and groups of the most sensitive and least sensitive animals were then treated chronically with ethanol. In both species, the most sensitive animals showed greater and more rapid development of chronic tolerance than did the least sensitive. (2) The same five rat strains that were used in the studies on voluntary consumption of ethanol (see Section 1 above) were treated chronically with large doses of ethanol. No systematic relation was found between their comparative initial sensitivities and the rate or extent of chronic tolerance development. These findings suggest that within a given strain or species, individual differences in initial sensitivity are a major determinant of tolerance development, as predicted by our hypothesis that the degree of functional disturbance produced by the drug constitutes the stimulus to tolerance development. On the other hand, in comparisons between strains or species, genetic factors may limit the capacity for adaptation regardless of the magnitude of the stimulus. The relationship between acute and chronic tolerance is currently being assessed.

Another important question relates to cross-tolerance between drugs with apparently similar effects, such as ethanol and barbiturates. A striking and unexpected finding in earlier work was the asymmetry of cross-tolerance among ethanol, pentobarbital, and chlordiazepoxide, which probably related to differences in their molecular mechanisms of action. That work has now been extended by parallel studies in four different strains of rat: Wistar, Sprague-Dawley, Long-Evans, and Holtzman. In all cases, when tolerance to ethanol was produced by simple exposure to high doses, it was accompanied by only minimal cross-tolerance to pentobarbital and no change in pentobarbital pharmacokinetics. On the other hand, chronic pentobarbital treatment resulted in definite cross-tolerance to ethanol. When ethanol tolerance was facilitated by Pavlovian conditioning to a specific environment associated with alcohol administration, cross-tolerance to pentobarbital *was* encountered in that environment in all four strains.

Similarly, when rats were made to perform a motor coordination task (the moving-belt test) under the influence of a large dose of ethanol every four days, they became tolerant to the impairing effect of ethanol, as well as to its hypothermic and hypnotic effects, and also cross-tolerant to motor impairment by pentobarbital. The same dosage of ethanol, without the opportunity for intoxicated practice, produced tolerance to ethanol but no cross-tolerance to pentobarbital. These findings suggest that facilitation of tolerance by Pavlovian conditioning, or by task practice in the intoxicated state, may involve additional neuronal mechanisms or pathways that may be shared by drugs with different molecular mechanisms of action. The effects of intoxicated practice and of environmental conditioning on tolerance to the treatment drug itself were found to be of critical importance when the treatment dose was small or medium, but not when it was large.

Three neurochemical lines of investigation into cellular mechanisms of alcohol tolerance, involving studies of the cell membrane ($Na^+ + K^+$)-activated adenosine triphosphatase

(ATPase), the interaction of a vasopressin-like brain peptide (DGAVP) and serotonergic neurons, and β-endorphin, were described in the last *Research Digest*. All three lines of research have continued during the past two years.

It was reported previously that lesioning the serotonergic fibre tracts from the median raphe nucleus to the hippocampus abolished the ability of DGAVP to maintain ethanol tolerance after chronic ethanol treatment was stopped. This finding suggested that DGAVP exerted its tolerance-preserving influence through some interaction with serotonin neurons in the hippocampus. One possibility was that DGAVP increased the synthesis and/or release of serotonin by these neurons. This possibility was studied by measuring the accumulation of the serotonin precursor, 5-hydroxytryptophan (5-HTP), within the hippocampus when the enzymatic conversion of 5-HTP to serotonin was blocked by a selective inhibitor. Neither acute nor chronic administration of DGAVP (the latter being shown to maintain ethanol tolerance in these same rats) had any effect on the turnover rate of 5-HTP or serotonin *in vivo*. Addition of DGAVP to isolated hippocampal slices *in vitro* also failed to increase the release of serotonin in response to stimulation by potassium. The possibility of a post-synaptic interaction of DGAVP and serotonin on the same target sites is now being studied.

In earlier work, it was found that ethanol tolerance was accompanied by an increased rate of synthesis and release of β-endorphin by the neurointermediate lobe of the rat pituitary gland, as studied *in vitro*. Since changes in the pituitary might not reflect corresponding changes in the brain itself, the study has been repeated with the latter focus. Rats were made chronically tolerant to ethanol, and β-endorphin levels were then measured by radioimmunoassay in tiny samples of tissue from eleven different regions of the brain, as well as in the pituitary and blood plasma, on the last day of ethanol treatment and days 1, 3, 8, and 15 after ethanol withdrawal. Several regions, including the arcuate nucleus of the hypothalamus (where brain β-endorphin is produced), amygdala, periventricular thalamus, and pre-optic periventricular hypothalamus, showed a pattern of fall in β-endorphin levels during withdrawal that was maximal on day 3 and had returned to baseline by day 8 or 15. Similar disturbances of other opioid peptides, the enkephalins, are now being studied.

In the last *Research Digest* an extensive description was given of studies on the relation between alcohol tolerance and the activity of the neuronal membrane ATPase, its inhibition by ethanol, and sensitization of this inhibitory effect by norepinephrine, in different regions of the rat brain. It has now been shown that the same ethanol-norepinephrine interaction with the cell membrane ATPase occurs in heart and kidney, but not in liver. An extensive program of further research on the specificity of this interaction, and of its possible role in either the production or the expression of tolerance, had been planned but was interrupted by the sudden and very premature death of the key biochemical researcher on this project, Mr. Narayan Rangaraj. The work will be resumed shortly, when a new biochemist is recruited.

Physical dependence is generally thought to be a different manifestation of the same cellular adaptive changes that underlie tolerance, and therefore the signs of drug withdrawal are generally pictured as being opposite in direction to those of the acute action of the drug in question. However, certain opiate withdrawal signs do not fit this concept. Studies were therefore undertaken of the effects of direct injection of mu, kappa, and sigma opioid agonists into different regions of the hippocampus. The acute effects, especially of kappa and sigma agonists, included "wet-dog shakes," salivation, piloerection, and other signs that are usually considered characteristic of withdrawal rather than of the acute action of opiates. Kindled seizures in the hippocampus produced similar behavioral signs. These findings suggest a radically new concept: that the "withdrawal reaction" is actually due to an imbalance of agonist action at the different opioid receptor types in the hippocampus, when mu agonists (e.g., morphine and heroin) are lost rapidly from the mu receptors but continue to act for a longer time on the kappa and sigma receptors. Further experiments are planned to test this hypothesis.

Investigators: H. Kalant, J.M. Khanna, A.D. Lê, M.A. Linseman, N. Rangaraj, M. Speisky

4. Studies on Drug-Related Brain Damage

In earlier work it was found that continuous feeding of ethanol to rats, either in a liquid diet or by stomach tube, in daily doses that produced early and marked development of tolerance, gave rise after 3–4 months to a gradual but complete loss of tolerance despite continuation of the same dosage. It was suggested that the loss of tolerance might be an early indication of alcoholic brain damage. The experiments have now been repeated, and the late loss of tolerance has been confirmed, but the rats did not show any impairment of spatial-temporal learning in the radial-arm maze, which is a sensitive indicator of brain damage in the hippocampus. This line of research is temporarily in abeyance, until other suitable tests of minimal brain damage in rats can be set up.

Investigator: J.M. Khanna

5. Development of New Microanalytical Methods

This department enjoys the benefits of having a staff member with considerable expertise in the area of high performance liquid chromatography (HPLC). This technique lends itself readily to the rapid, accurate measurement of extremely small quantities of many drugs and naturally occurring substances in body fluids and tissues. HPLC methods using electrochemical detection have been developed in the Drug Analysis Laboratory for a number of the studies referred to in this report. During the past two years, three such methods have been developed for:

1. simultaneous measurement of norepinephrine, serotonin, dopamine, and the four major metabolites of these, in milligram-size samples of brain tissue;
2. measurement of methionine enkephalin and leucine enkephalin in picogram amounts (a picogram = one billionth of a milligram) in brain tissue samples;
3. measurement of the major cannabinoids (THC, CBD, CBN, and CBC) in blood plasma at levels that would be found in humans after the smoking of marijuana.

These methods have been invaluable in the conduct of the research described above, and have also been reported in international journals for the benefit of other researchers in this and related fields.

Investigators: H.Kalant, J.M. Khanna, C. Kim, M. Speisky

CLINICAL INSTITUTE DIVISION

The Clinical Institute was established in 1971 as a Group L Hospital under the Public Hospitals Act to treat patients suffering from alcohol- and drug-related problems. In addition to providing treatment, it is the Foundation's major resource for clinical research, with thrusts into the causes and consequences of alcohol and other drug dependence, and the improvement of existing treatments and development of new ones. The major focus of research is in the biomedical and sociobehavioral areas, where studies are concerned with the early identification, prevention, and treatment of such major alcohol- and drug-related problems as excessive alcohol consumption, liver disease, brain damage, alcohol withdrawal, sociobehavioral problems, tobacco dependence, benzodiazepine abuse, opioid dependence, and multiple drug use. The research objectives of the Clinical Institute are the following:

1. To conduct basic research concerning the pathogenesis of biochemical, biomedical, and behavioral antecedents and consequences of alcoholism and other drug dependence disorders.
2. To conduct clinical research concerning the nature and genesis of biomedical and behavioral antecedents and consequences of alcoholism, tobacco dependence, and other drug dependence disorders in humans, which may lead to new and more effective, efficient, or rational treatment tactics.
3. To conduct treatment research that is scientifically sound, does not expose patients to unacceptable hazards or risks, and has the potential:
   (a) to develop new treatment approaches that are more effective, more efficient, and safer or less costly than existing treatments, and that can be applied to large groups of patients in the evolving health care system.
   (b) to determine the efficacy or safety of unproven treatments.

Research programs ranging from basic studies to treatment evaluations in the Clinical Institute have specifically resulted in the development of new approaches in the early detection and treatment of alcohol and drug dependence.

E.F. Watson
Director, Clinical Institute Division

BIOMEDICAL RESEARCH
Program Manager: R.C. Frecker

The Biomedical Research program comprises four sub-programs with distinct disciplinary orientations — Clinical Pharmacology, Gastroenterology, Neurology, and Psychiatry. Work done within these groupings employs the methodologies of areas ranging from cellular neurophysiology and biochemical pharmacology, through biomedical engineering, to treatment research and clinical epidemiology. What binds these diverse programs together is the common focus on significant clinical problems related to substance dependence.

The more basic research is driven by the need for a better understanding of particular clinical entities such as brain or liver damage associated with alcohol abuse, or withdrawal states resulting from chronic administration of alcohol or other drugs. The more applied (clinical and treatment) research is related to the elaboration of clinically relevant models of treatment and their evaluation in a clinical or treatment setting. By using such an approach, scientists in this department expect to provide tools for both the prevention of substance abuse disorders themselves and their treatment.

Most groups enjoy regular collaboration with programs in other areas. Of particular note is the longstanding and successful collaboration between Gastroenterology and Biochemical Research relating to liver pathology, and the collaborative research done by both Clinical Pharmacology (benzodiazepines, tobacco) and Neurology (alcohol-induced brain damage) with scientists in Sociobehavioral Research. More recently the Clinical Pharmacology and Neurology programs have been developing several collaborative research projects particularly with respect to the neuropharmacological mechanisms of the dependence on alcohol and other CNS depressants and new pharmacotherapies for attenuating the Korsakoff amnesic syndrome. Although a large proportion of effort in Biomedical Research relates to the causes and consequences of excessive alcohol use, its prevention, and its treatment, a major interest exists in benzodiazepines and tobacco. Other foci relate to generic issues of psychoactive drug interactions and the management of drug withdrawal and to other drugs liable to be abused, such as solvents, barbiturates, and opiates.

Research in the biomedical area relates primarily to the Foundation's goal to develop improved treatments for substance abuse disorders through an analysis of current treatment methods, tested against knowledge gained through research. By systematic evaluation of potential new treatments, researchers in this area have been successful in relating a basic understanding of the causes of drug dependence, and its consequences, to the development of treatments that are models for the health care system.

CLINICAL PHARMACOLOGY
Program Manager: C.A. Naranjo

This program focuses on the identification, assessment, and treatment of dependence, particular emphasis being placed on alcohol, benzodiazepines, and tobacco. Mechanisms are sought to explain both acquisition and maintenance of drug use, from which study it is hoped to derive better means of achieving moderation or abstinence. Innovative approaches to the treatment of withdrawal syndromes have been developed, and are assessed using a variety of techniques that measure clinical effect and therapeutic response in patients. An underlying rationale is to develop simplified but effective treatments that are easily adaptable to general medical practice.

The major lines of research in Clinical Pharmacology are:

1. The pharmacotherapy of alcoholism: Research in this line is aimed at improving the treatment of the alcohol withdrawal syndrome and at testing new neuropsychopharmacological interventions for decreasing alcohol intake.

2. Clinical pharmacological methods for assessing the abuse potential of psychoactive drugs: The major research focus is benzodiazepine dependence; methods for testing dependence liability of new anxiolytic agents have been developed.

3. The assessment of the clinical toxicity of psychoactive drugs: Particularly important are the studies for assessing the pharmacodynamic and pharmacokinetic interactions of ethanol and other psychoactive drugs (e.g., benzodiazepines and antidepressants). We are also testing new standardized diagnostic instruments for assessing adverse drug reactions and other drug-related problems.

4. Smoking research: The aim of this line of research is to develop a better understanding of the factors that govern the acquisition, maintenance, and cessation of tobacco use, and to develop more effective treatments for reducing the hazards associated with this habit — through either prevention or treatment strategies aimed at cessation.

1. Pharmacotherapy of Alcoholism

The pharmacotherapy of alcoholism was stagnant some years ago. Several drugs were (and are) used without our having an appropriate rationale for such use. A group undertook the task, about five years ago, of identifying potential areas where improvements in drug therapy in alcoholism could be accomplished either by rationalizing the use of the drugs currently available (e.g., see projects in the alcohol withdrawal syndrome and the alcohol-sensitizing drugs) or by attempting innovative approaches to drug therapy (e.g., use of serotonergic drugs for moderating ethanol intake). Thus, a number of studies have been conducted in both areas. The alcohol withdrawal syndrome projects have resulted in better understanding of the contribution of non-pharmacological and pharmacological interventions for achieving effective drug therapy. In addition, new assessment procedures and standardized treatment approaches have greatly improved and simplified the therapy of this condition. The findings have occasioned an award from the Canadian Society for Clinical Pharmacology in 1984 for outstanding clinical research and have also been adopted in various treatment centres in Canada and around the world. Our treatment protocols are currently considered the "gold standard" pharmacotherapy of the alcohol withdrawal syndrome.

In the development of innovative approaches for achieving abstinence of moderate alcohol drinking, the group has continued the testing of new strategies for old drugs (e.g., relapse prevention techniques used in conjunction with calcium carbimide; see studies by J.E. Peachey and H.M. Annis described elsewhere).

The development of innovative approaches using serotonergic drugs is ongoing. The hypothesis that drugs that enhance serotonergic neurotransmission attenuate ethanol intake has been supported by a number of consistent findings in animals and humans, reported by our group and other investigators. Serotonergic neurotransmission can be enhanced by several pharmacological approaches: for example, loading with serotonin precursors such as tryptophan and 5-hydroxytryptophan, using serotonin releasers (e.g., viqualine), using serotonin re-uptake inhibitors (zimelidine, citalopram, viqualine, fluoxetine, etc.), or using 5-HT agonists (MK–212, quipazine). Although these manoeuvres reduce ethanol intake, only the serotonin re-uptake inhibitors are available for human use. Therefore, our studies in early-stage problem drinkers have examined the use of these agents. The potential clinical relevance of these findings became apparent by our recent demonstrations that zimelidine and citalopram, both specific serotonin re-uptake inhibitors, attenuated ethanol intake in non-depressed heavy drinkers. These findings have stimulated clinical research in this area by other investigators around the world. The serotonin re-uptake inhibitors are particularly interesting compounds, for studies conducted at the National Institute on Alcohol Abuse and Alcoholism suggest that these agents may also attenuate ethanol-induced memory impairments, and they do not seem to interact either aversively (as do, for example, alcohol-sensitizing drugs) or adversely (e.g., inducing psychomotor impairment) when given in conjunction with alcohol. Therefore, further testing is designed to identify the most effective and safest of these agents for application as an adjunct in the treatment of problem drinkers. Studies are aimed particularly at the determination of the dose-response relationship and the elucidation of the importance of specificity of effects.

The methodology developed for the testing of serotonergic agents can now also be applied to the testing of other drugs interacting with other neurotransmitter systems.

Pharmacotherapy of Alcohol Withdrawal. The goal of this research continues to be the development of treatments for alcohol withdrawal based on a sound pharmacodynamic and pharmacokinetic rationale.

A series of studies involving more than 300 patients has resulted in a marked simplification of the usual treatment of alcohol withdrawal. The highlights of this work include:

1. Development of a simple, valid, and reliable clinical scoring system that can be used by medical and paramedical staff to follow the clinical severity of withdrawal.
2. Determination of the components and importance of supportive (i.e., non-pharmacological) care in treatment of withdrawal. Such care is effective alone in 85%, 74%, and 47% of emergency room clients, inpatients without medical complications, and inpatients with medical complications respectively.
3. Demonstration that supportive care does not prevent the appearance of late complication of withdrawal in hospitalized medical patients.
4. Demonstration that virtually all patients can be treated effectively with diazepam given orally. More than 50% are treated within seven hours and require only three 20 mg doses of drug. No further drug therapy is necessary.
5. Demonstration that, when the loading dose approach is used, no further drug therapy is needed because of slow diazepam elimination from the body.
6. Provision of a large body of clinical data indicating that phenytoin is usually not required in patients with a history of withdrawal seizures if diazepam is given as above.

The resulting treatment procedure is safe and effective and simplifies and greatly shortens the usual four- to five-day treatment procedure.

Mechanism and Treatment of Withdrawal from Alcohol, Benzodiazepines, and Other Drugs. The goals of this research are:

1. To determine the selectivity and specificity of current pharmocotherapies in drug withdrawal.
2. To develop animal models that will help identify the pharmacological basis of improved therapy for alcohol, benzodiazepine, and other drug withdrawal.
3. To determine the functional importance of the proposed GABA-benzodiazepine-barbiturate receptor model.

During past years a major effort was directed at determining whether there is any pharmacological rationale to the clinical

practice of giving prophylactic phenytoin (an anticonvulsant drug) in addition to diazepam to patients in alcohol withdrawal who have a history of withdrawal seizures. In contrast to this common practice, our own clinical observation suggested that diazepam is sufficient. Our experiments with rodents during alcohol withdrawal indicated that diazepam is a potent anticonvulsant for spontaneous as well as for picrotoxin-induced seizures. For animals in alcohol withdrawal, diazepam is even more effective than phenytoin; that is, the animals are more sensitive to diazepam effects in withdrawal.

These observations have direct clinical implications. If confirmed in the human they would provide further evidence that the treatment of the alcoholic in withdrawal need not include phenytoin unless the patient has a history of epilepsy.

More recent studies are exploring the effect of calcium-channel agonists and antagonists on the development of the alcohol dependence syndrome and the manifestations of the alcohol withdrawal syndrome. Other studies have looked at the determinants of the specificity and selectivity of drug therapy in the alcohol withdrawal syndrome.

New Neuropsychopharmacological Treatments for Decreasing Ethanol Intake. This research seeks to identify new drugs that might decrease ethanol intake and therefore could be used as adjuncts to psychosocial interventions in the treatment of problem drinkers.

A study to determine the effects of zimelidine on alcohol intake was reported in *Research Digest 1982–84*. Zimelidine-induced variations in ethanol intake were characterized by an increase in the number of days of abstinence and a decrease in the number of drinks consumed.

Since zimelidine was withdrawn from the market because of toxicity, we are now systematically testing other drugs that enhance serotonergic neurotransmission in order to identify the most effective and safest agent to decrease alcohol consumption. A recent study has confirmed that citalopram, the most specific and selective serotonin re-uptake inhibitor, also attenuates ethanol intake in early problem drinkers. These studies support the notion that serotonin and serotonin-altering drugs play an important role in regulating ethanol intake in humans. Other studies are assessing the clinical effects of viqualine and fluoxetine in early-stage problem drinkers. Future studies will assess the role of these drugs as adjuncts in the treatment of problem drinkers.

Investigators: C.A. Naranjo, E.M. Sellers, P.Wu

2. Clinical Pharmacological Methods for Assessing the Abuse Potential of Psychoactive Drugs

Research in this area has concentrated on the assessment of the dependence liability and problems associated with chronic use. These clinical studies were initiated because of the high prevalence of long-term benzodiazepine use. Also, there was a lack of clinical data on different aspects of the benzodiazepine withdrawal syndrome such as uncertainty concerning the clinical management of this syndrome. In addition, the problems associated with long-term benzodiazepine abuse were not adequately characterized. The projects undertaken in this area have been most successful in providing clinically relevant answers concerning these aspects. In addition, a battery of clinical instruments for assessing withdrawal symptoms and treatment outcome has been developed. These findings can be applied to the testing of newly developed non-benzodiazepine anxiolytic agents, which are now being marketed in Canada and abroad.

The most important finding of this project was the development of a loading-dose tapering approach for treating subjects withdrawing from high doses of benzodiazepines. Also, we completed the first well-controlled, randomized double-blind study that shows conclusively the presence of withdrawal symptoms after abrupt cessation of chronic use of benzodiazepines at therapeutic doses. These findings should have a major impact in the clinical use of this group of drugs.

Benzodiazepine Dependence: Assessment of Behavioral Toxicity, Physical Dependence Liability, and Experimental Behavioral Treatment — Clinical Pharmacological Aspects. This research program seeks to provide a good description of the patterns of benzodiazepine use and abuse by studying patient characteristics and factors associated with this phenomenon. The purpose is to identify the problems of cessation (including withdrawal syndrome) in long-term benzodiazepine users, and to identify the behavioral toxicity and other side effects associated with long-term use.

Data on drug use and other clinical characteristics have been collected in 163 patients referred to the Foundation for treatment of benzodiazepine abuse. Two distinct patterns of abuse have been identified: benzodiazepines were the only drugs of abuse for 56% of these patients, whereas the balance were multiple drug abusers. Patients using only benzodiazepines were older and took lower doses of drugs for longer periods of time than multiple drug abusers.

High-dose benzodiazepine abusers can be safely and effectively detoxified in hospital, by gradual reduction of diazepam. Patients abusing only low doses of benzodiazepines are treated as outpatients with a diazepam tapering-off regime and cognitive reappraisal therapy.

The identification of two different groups of benzodiazepine abusers has implications for the assessment, treatment, and outcome of these patients. Results of experimental treatments will help determine the best treatment approaches, while results of the characterization of benzodiazepine withdrawal syndrome will help toward a better identification and treatment of this phenomenon. This study is being done in collaboration with the Biobehavioral Research program.

Investigators: U. Busto, E.M. Sellers, C.A. Naranjo

3. The Assessment of the Clinical Toxicity of Psychoactive Drugs

Clinically Important Pharmacokinetic Interactions of Ethanol and Drugs. The goals of the research are to determine if alcohol-induced increased systemic bioavailability accounts for the marked interaction of alcohol with many drugs; to determine the characteristics of drugs susceptible to such an ethanol systemic effect on hepatic clearance; and to characterize the

magnitude of the interaction using sensitive measures of drug effect.

Studies have examined the interaction of ethanol with diazepam, amitriptyline, propranolol, triazolam, lorazepam, oxazepam, propoxyphene, and, more recently, zimelidine, viqualine, and fluoxetine in humans. These studies have identified a new mechanism whereby alcohol can increase concentrations after their oral ingestion. Ethanol markedly inhibits uptake and biotransformation of some drugs, with the result that the drug concentration during absorption may increase by up to 200% when ethanol is present. Such increases in concentration can be expected to augment markedly the toxic effects in such situations as drug overdose and poisonings. Ethanol effects are most pronounced for high-extraction drugs with long half-lives, such as amitriptyline. In addition, these studies have suggested that individual variations in central nervous system "sensitivity" are important determinants of the pharmacodynamic effect. It may be possible to determine why for some individuals ethanol profoundly enhances the effects of other drugs.

These studies have established a reliable methodology for studying drug interactions. They may also have explained why ethanol in combination with some drugs (e.g., amitriptyline, propoxyphene) can have such serious, sometimes lethal, effects in the human. Patients should be made aware of the danger of such interactions.

In addition, the adverse kinetic and dynamic interactions between ethanol and serotonin uptake inhibitors (zimelidine, viqualine, fluoxetine) have been studied. The results indicate that serotonin uptake inhibitors do not interact to a clinically important extent even though ethanol may produce increases in drug concentration. The combination of ethanol and serotonin uptake inhibitors usually produces only slightly more psychomotor impairment than either treatment alone. Subjects receiving serotonin uptake inhibitors and ethanol did not show clinical, physiological, or biochemical evidence of an acetaldehyde-mediated aversion reaction.

Serotonin re-uptake inhibitors are being tested clinically for their effects on ethanol intake. These studies provide further information to define the clinical use of these drugs particularly with respect to their efficacy, safety, and mechanisms of action.

Standardized Diagnostic Procedures for Assessing Adverse Drug Reactions and Other Drug-Related Problems. The diagnosis of adverse drug reactions (ADRs) to psychoactive agents and other drugs is a difficult problem. Some years ago our group developed an algorithm for assessing ADRs in a variety of clinical situations. This method proved itself useful, simple, and popular. In subsequent years, other researchers have also developed similar instruments. Therefore, the need arose to develop a consensus instrument that could be generally applied. An international group of scientists (from the universities of Toronto, McGill, Minnesota, and Georgetown) working in the area agreed to collaborate in a project for achieving such a goal.

We have recently succeeded in developing a new Bayesian Adverse Reactions Diagnostic Instrument (BARDI). This instrument is based on prescriptive probability theory, and it has been successfully applied in a variety of clinical situations. Studies for assessing the application of BARDI to the assessment of the clinical toxicity of new drugs are under way.

Similar Bayesian approaches will be used in the diagnosis of drug abuse in elderly patients and for the assessment of inter-individual variations in drug efficacy. In addition, studies for assessing the variations in the pattern of utilization of psychoactive drugs and their relations to drug-related problems are being studied (in collaboration with Dr. U. Busto of the pharmacy research program).

Investigators: U. Busto, C.A. Naranjo, E.M. Sellers

4. Smoking Research

Research on tobacco is conducted as a collaborative effort by the Clinical Pharmacology program, the Institute of Biomedical Engineering (IBME, University of Toronto), and the behavioral pharmacology program. The biomedical and instrumentation aspects of research into tobacco dependence will be described here; other aspects of this research are described under the Biobehavioral Research program.

Instrumentation to Measure the Pharmacological Effects of Tobacco Constituents on the Human Central Nervous System. The goals of this research are to develop sensitive, selective, and non-invasive pharmacodynamic measurement systems for detecting and quantifying the effects of nicotine and other smoke constituents on the human central nervous system; to evaluate systematically the diverse sources of variability inherent in such measurements — including instrumental and various rhythmic variations in response inherent to normal physiological control mechanisms; and to determine empirically the optimal composition of complex dependent variables to "tune" the pharmacodynamic measurement system for drug sensitivity (maximal signal/noise ratio) and selectivity (maximum specificity of response for given tobacco constituents).

The Clinical Pharmacology Tobacco Research Group has available to it the resources of the Clinical Research Facility, which includes the Clinical Research Unit, the Human Responses Laboratory, and the Behavioral Responses Laboratory. Studies may be conducted on an inpatient or outpatient basis. Useful measures include hand tremor, heart rate, standing steadiness, skin temperature, and a variety of indices of visual information processing (flicker sensitivity, evoked potentials, and eye movements), and a variety of observational techniques of smoking typology. Through collaboration with the University of Toronto (IBME) a novel eye-movement measurement system has been developed. The precision and accuracy of this device will permit a millisecond-by-millisecond examination of the brain's response to administered tobacco constituents (e.g., nicotine), within a frame which will permit puff-by-puff analysis of the effects of inhalation of tobacco smoke or other nicotine-containing aerosols; or the instantaneous measurement of the effects produced by other routes of administration. Tolerance effects in naive subjects, withdrawal effects in dependent subjects, and the modulation of effect in regular smokers will all be examined within the bounds of ethical propriety.

A better understanding of the basic mechanisms underlying tobacco dependence is sought. Instrumentation development has reached the stage where clinical investigation is possible. This

research will characterize better both the phenomenology and neuropharmacology of dependent smokers under various conditions of nicotine exposure and deprivation. These studies will lead to an evaluation of different treatments which, amongst other strategies, will employ nicotine-containing chewing gum.

Chemical Analysis of Tobacco Constituents in Smoke and Other Aerosols and in Plasma and Other Biological Samples. The purposes of this research are to develop chemical assays that permit the quantitative measurement of nicotine and cotinine concentrations at the levels normally present in plasma and other biological samples; to determine nicotine, carbon monoxide, and "tar" yields from cigarettes under conditions of standard machine smoking and of nicotine deliveries from a novel sub-micron aerosol generator that seeks to simulate human smoking behavior; and to survey the constituent yields of cigarettes collected from a variety of developing nations in collaboration with the World Health Organization, in an effort to better understand tactics the tobacco industry may employ to assure effective market penetration.

A new "clean air" (nicotine-free) laboratory is available in which concentrations of nicotine and cotinine can be determined. A "tobacco science" laboratory that meets international standards has been set up and permits analysis of cigarette yields. To date, 50 brands of cigarettes have been analysed and compared to companion brands sold in developed countries. A detailed report of these analyses is shortly to be released by the World Health Organization.

The use of plasma nicotine and cotinine assays is prerequisite to the conduct of meaningful pharmacological investigations of tobacco dependence. It will become necessary over time to develop assays for other constituents in other biological and non-biological samples. The demography of cigarette constituent yields may afford a better understanding of factors governing acquisition and maintenance of the tobacco habit in less experienced (relatively drug-naive) populations. Additionally, ongoing surveillance can be expected to have the effect of making the tobacco industry more conscious that their marketing policies are the subject of public concern, and may further motivate government to take effective political action to control the marketing of tobacco, the use of which has proven inimical to public health.

Investigator: R.C. Frecker

GASTROENTEROLOGY
Program Manager: H. Orrego

The focus of this program's research continues to be alcoholic liver disease. Specific projects investigate the pathogenesis of alcoholic liver disease and the development of parameters both to evaluate disease severity and to determine the prognosis. A strong liaison exists with the Biochemical Research program, and effective linkages have been forged that permit the transfer of more basic research into the clinical environment. The overall goal is the development of new forms of treatment for this important complication of alcohol abuse, treatment that is firmly based on sound scientific principles and rigorous clinical evaluation. Three major lines of research endeavor are identified, and the projects in association with each are described:

1. Clinical evaluation and treatment of alcoholic liver disease;
2. Clinical research relating to portal hypertension and portal systemic encephalopathy;
3. Investigations into the pathogenesis of alcoholic liver disease, and interaction between alcohol and anesthetic agents.

1. Clinical Evaluation and Treatment of Alcoholic Liver Disease

There has never been a good system of parameters to assess the prognosis and the severity of alcoholic liver disease (ALD). Without such a system, the determination of the efficacy of treatments and the possibility of correlating biological events with the severity of liver disease are both seriously curtailed. In the case of clinical trials, most of the published findings have been confined to the effects of treatment on mortality. This approach has the drawback that, in order to avoid risk of a statistical error, one has to use either an enormously large number of patients with a moderate mortality, or groups of patients with very severe forms of the disease and extremely high mortality. Results from the latter group might not be applicable generally to the disease.

Furthermore, if we were to look at the full range of severity of the disease, without an adequate stratification of the disease spectrum, effectiveness of a treatment operating in one stratum may be masked by the variation of the whole.

The prognostic significance of a battery of commonly used clinical, laboratory, and histological indicators of liver dysfunction was assessed in relation to mortality risk in a one-year follow-up study of 253 patients with alcoholic liver disease, of whom 51 died within such time. A number of abnormalities were found to be statistically associated with a higher risk of death; these were analysed in order to determine their relative mortality risk (RR). RRs are calculated by dividing the percentage mortality in those with the abnormality by the percentage mortality in patients without it. All of the analysed parameters, when used individually as predictors of mortality, showed shortcomings that made them unreliable as markers of severity except at very advanced stages of the disease. However, when these mortality risks are added, the resulting combined clinical and laboratory index (CCLI) has a quasi-linear relationship with the risk of mortality for the complete population. Obtaining a single severity score such as the CCLI is of value in (a) assessing the effectiveness of treatment modalities; (b) analysing the success of randomization; (c) separating cohorts of different severity; and (d) comparing new liver tests, histological abnormalities, or specific biological events with the severity of alcoholic liver disease.

The RR factors for mortality associated with the histological alterations were lower than those derived from clinical or laboratory measurements. These data showed that the classical categorization of ALD according to fatty liver, alcoholic hepatitis, and cirrhosis has only a very limited value as a functional division. However, we have now found that combining the significant histological features produces a combined morphological index (CMI) that has enabled us to assess the magnitude of the impact of hepatitis on the mortality of cirrhosis and to show the relatively benign nature of cirrhosis *per se* in the absence of significant features of hepatitis.

The Gastroenterology program has undertaken a clinical trial to assess the efficacy of propylthiouracil (PTU) in the treatment of alcoholic liver disease. The use of PTU is based on the hypothesis that alcohol induces a hypermetabolic state in the liver, increasing the oxygen demands of the liver cells. When the supply of oxygen in the circulation is restricted (because of anemia, smoking, upper respiratory tract diseases, etc.), the increased demand for oxygen is not met and liver damage ensues. Experimentally, it has been shown that rats treated chronically with alcohol (presenting an increase in liver oxygen consumption) develop liver necrosis (cell death) when submitted to hypoxia (low-oxygen tensions) or to experimentally induced anemia. The alcohol-induced increase in oxygen consumption is thyroid-dependent and is abolished by removal of the thyroid gland or by drugs that inhibit the production of thyroid hormones, such as PTU. Experimentally, PTU has been shown to suppress the liver damage induced by the combination of alcohol and hypoxia in the rat.

A preliminary short-term (45-day) trial of PTU in alcoholic liver disease showed that better recovery occurred in patients receiving PTU than in patients receiving placebo. These results led to a more detailed study that entailed follow-up for a minimum of one year of a large number of patients. This study has just reached completion and is now in the process of analysis. Approximately 350 patients have been followed for six months, 315 for one year, 260 for two years, 220 for three years, and 130 for five years.

This study has resulted in an enormous mass of information on the natural history of alcoholic liver disease. It is probably the most complete and detailed follow-up study of patients with this condition in the world. Aside from the information on the effects of PTU in the treatment of alcoholic liver disease, the data from the follow-up study will result in several clinical publications on the general topic of alcoholic liver disease. For example, long-term survival of patients in both the acute trial of PTU and the present trial ($N = 518$) has been obtained. We have the death certificates of those patients who have died. This information will allow us to determine the accuracy of diagnosis

of cirrhosis on death certificates, the source of data on the incidence of cirrhosis in populations that is used by epidemiologists.

Although it might appear surprising, the literature on the effects of abstention from drinking on the severity of liver disease is not only very sparse but also contradictory. While some authors claim that continued alcohol intake results in deterioration, others claim that it has no effect on the severity of established alcoholic liver disease. Since the PTU trial is being controlled for drinking through determination of alcohol in urinary specimens provided on a daily basis by the patients, the effects of periods of drinking vs. periods of abstention on the severity of ALD, as measured by the CCLI (among placebo patients), are currently being analysed. These data should define clearly this unsettled problem. As well, we will be able to study the relationship between the degree of liver damage and alcohol tolerance.

A number of studies have shown a relationship between gamma-glutamyl transpeptidase (GGT) activity and alcohol consumption as determined by self-report. However, self-reporting has been shown to be unreliable. We have investigated this relationship in our patients, using their urinary alcohol levels to monitor alcohol consumption to see if GGT could be used by physicians treating patients with alcoholic liver disease in whom monitoring for alcohol consumption could be most important.

In another study, the effect of withdrawal on the severity of ALD is being examined. About 15% of ALD patients deteriorate after seven to fourteen days of being admitted to hospital. This period of increasing severity, which is followed by recovery, has been reported by many other investigators; some claim that it can occur in up to 50% of patients admitted with the disease. The cause of this deterioration is the subject of our study. Since withdrawal entails stress and is accompanied by increased action of catecholamines, cortisol, and glucagon, which have been shown to increase oxygen requirements of the liver, it appears possible that the increased need for oxygen in a liver that is already at risk because of the effect of alcohol could result in further hypoxia, cell damage, and necrosis, therefore worsening the clinical status of the patient. We are examining whether those patients in whom a deterioration occurs also have more severe withdrawal syndromes, and higher blood or urinary levels of the stress hormones, than a population in whom the deterioration is not observed. The study is a cooperative one with a large university hospital in Madrid. Thus far 30 patients have been studied in Spain and 50 at the Clinical Institute. All of these patients were drinking until the time of admission. The intensity of withdrawal has been assessed on a special index developed at the Foundation, the Clinical Institute Withdrawal Assessment (CIWA) score, while the CCLI has been used to assess liver function. Urinary catecholamines have been measured during the first seven days of hospital stay. Other biochemical measurements include fasting plasma glucagon and cortisol. The patients are followed up to 28 days after they have been admitted to the study. Positive findings would constitute grounds for research that might shed light on this unexplained and paradoxical reaction that appears to be a component of alcoholic liver disease. Data analysis is ongoing.

On the basis of work started by Israel et al. in the early 1970s, our group has proposed that alcohol-induced necrosis results from the interaction of the increase in liver oxygen consumption induced by ethanol and a decrease in O_2 delivery to the liver resulting from different causes. We have shown that rats, a species that normally does not present liver necrosis when fed alcohol chronically, do show liver necrosis when submitted to the combined effects of chronic alcohol and hypoxia, or anemia. Such a relative liver-hypoxic state can be accentuated in several physiological and pathological conditions. Alcoholics are exposed, with a higher frequency than normal individuals, to a variety of situations that lead to a reduction in liver oxygenation, including respiratory and pulmonary dysfunction, pneumonia, and anemia due to nutritional and metabolic effects. Multiple additive combinations of these factors are likely to occur in alcoholics. The requirement of a combination of ethanol plus a reduction in O_2 supply to the liver for necrosis to occur might explain why not every alcoholic has Zone 3 necrosis, as an increase in the rate of oxygen consumption is not by itself sufficient to cause cell death. Anemia, one of the most prevalent abnormalities in alcoholic hepatitis, has the potential to be one of these precipitating factors that result in Zone 3 necrosis. We therefore have analysed its prognostic significance in patients with alcoholic liver disease. The prognostic significance of low hemoglobin levels was analysed in 253 patients followed for one year and monitored for 19 clinical and biochemical abnormalities characteristic of alcoholic liver disease. By stepwise discriminant analysis or logistic regression respectively, low hemoglobin was selected among the two or three independent laboratory discriminators for the risk of mortality. Patients with hemoglobin levels between 75% and 90% of normal (average 78.5 $\pm$ 1.5) showed a mortality rate of 47%. Strikingly, the mortality rate of patients with hemoglobin levels below 75% of normal was sevenfold higher than that of patients with near-normal hemoglobin levels (79% vs. 11% respectively). In this regard, it is noteworthy that alcoholic liver desease has been shown to be more serious in women in the reproductive ages; because of menstruation, their hemoglobin levels are lower than those of men and of postmenopausal women. Thus, it is likely that in human alcoholics, as is the case in rats, anemia might also constitute a cause of necrosis, rather than being always a consequence of liver disease. This concatenation of anemia leading to necrosis and thus to increased liver dysfunction and further anemia could represent a vicious circle. We propose now to relate the degree of hypoxia, as assessed by arterial blood gas measurements, with the degree of clinical and chemical abnormalities, as assessed by the Combined Clinical and Laboratory Index (CCLI) and, where possible, by the degree of "activity" on the liver biopsy as assessed by a newly developed Combined Morphological Index (CMI) and the degree of collagenization of Disse space as assessed by electron microscopy.

Another study, undertaken in collaboration with Dr. M. Sherman of the Toronto General Hospital, is concerned with the prevalence of occult hepatitis B virus infection in alcoholic patients with liver disease. The aim of this project is to investigate some aspects of HBV infection in patients with alcoholic liver disease and in patients with HBsAg negative chronic hepatitis and cirrhosis. In particular, these studies will aim to (a) determine the prevalence of occult HBV (i.e., HBsAg negative) infection in

alcoholic patients; and (b) determine whether the serological response to replicating HBV is different in alcoholics, with and without liver disease, from the response in normal non-alcoholic patients. Nalpas et al. suggest that some alcoholics do not mount an efficient antibody response to viral antigens and that this is not influenced by the presence of liver disease. Until recently the presence of viral replication has been defined by serological criteria only, but with the advent of molecular hybridization the presence of serum HBV DNA is now also accepted as an indication of replicating virus, although this criterion has not yet been correlated with the presence of replicating virus in the liver. A future study will determine the state of viral replication in alcoholic patients and correlate viral replication with the patients' serological status.

Relationship between Blood Acetaldehyde Concentrations after Alcohol Administration and the Severity of Alcoholic Liver Disease. Numerous studies have implied the role of acetaldehyde in many ethanol-induced alterations of hepatic function and structure. Mole for mole, the biological system is as much exposed to acetaldehyde as to ethanol. Acetaldehyde is reactive and toxic and binds non-enzymatically to phospholipids, amino groups of amino acid residues, and sulfhydryl groups. Acetaldehyde reacts with serotonin, dopamine, and norepinephrine to yield pharmacologically active compounds. The reaction of acetaldehyde with free amino acids of proteins could modify hepatic function. These alterations could include displacement of ligands from binding sites, interference with the activity of some enzymes, and inhibition of hepatic protein secretion. Acetaldehyde may play a role in immunological reactivy in alcoholic liver disease. Recently, acetaldehyde has been shown to stimulate collagen and non-collagen production by fibroblasts, in humans, and myofibroblasts in the baboon. Therefore, acetaldehyde may also play a role as a possible mechanism of fibrogenesis in alcoholic individuals. It is likely that many of the adverse actions of acetaldehyde will be potentiated in conditions that result in increased circulatory concentrations of acetaldehyde, resulting in a vicious circle of increasing liver damage in persons consuming alcohol.

In normal conditions, after ethanol is consumed, most acetaldehyde is not only formed in the liver but is also immediately oxidized there, so that little enters the blood of normal subjects. In alcoholics given infusions of ethanol, however, higher blood levels of acetaldehyde have been reported. A primary abnormality of acetaldehyde metabolism predisposing to alcoholism has been suggested to explain this difference. It has been found that the increased production in chronic alcoholics does not result from an increased rate of formation from ethanol but rather from a reduction in aldehyde dehydrogenase activity, which appears to be rate-limiting for hepatic oxidation of acetaldehyde. Although a marked reduction in liver acetaldehyde dehydrogenase has been reported in alcoholic cirrhosis, there is no information on acetaldehyde blood concentrations after alcohol intake in patients with various degrees of alcoholic liver disease, nor on the effect of the clinical severity of the disease in the acetaldehyde concentrations that result from alcohol metabolism.

We are currently studying the effect of liver dysfunction (severity of alcoholic liver disease) on acetaldehyde concentrations after a standardized dose of ethanol. Our group is in a very good position for this type of analysis. We are currently following a large number of patients with liver disease presenting with a wide range of severity. In most of these patients we have performed liver biopsies, and thus we have information on the morphological characteristics of their liver disease. We also have good information on their past drinking histories, and for many of them we have monitored alcohol intake from daily urinary alcohol determinations for many months or years. From these data we know that the majority of our patients are still drinking varying amounts of alcohol. The Combined Clinical and Laboratory Index (CCLI) permits an accurate assessment of the severity of alcoholic liver disease, and the Combined Morphological Index (CMI) allows a similar analysis of liver biopsies. We also intend to relate blood acetaldehyde concentrations to the rate of alcohol metabolism. In alcoholic patients with liver disease the concentrations of blood acetaldehyde could be expected to be influenced by a set of two factors: its rate of formation from alcohol (the rate of alcohol metabolism), and the capacity of the organism to metabolize acetaldehyde (acetaldehyde dehydrogenase).

The last three projects are oriented to the idea of trying to establish a reason for the very different evolutions and degrees of liver damage that can occur in individuals drinking the same amounts of alcohol for similar periods of time. Knowledge in this area might have projections in prophylaxis and in the detection of subjects at a higher risk of alcoholic liver disease. Of course, this type of information could also have therapeutic implications.

Investigators: L.M. Blendis, H.G. Giles, Y. Israel, H. Orrego, E.I. Vidins

2. Clinical Research Relating to Portal Hypertension and Portal Systemic Encephalopathy

Portal hypertension is one of the most important determinants of mortality in alcoholic liver disease (72% of deaths in our experience). Portal hypertension leads to the development of a vast system of collateral vessels that shunt the portal blood away from the liver and into the territory of the general circulation. This phenomenon has two effects: (a) veins forming part of this collateral network dilate and, in the case of the esophageal veins, can burst, leading to the high-mortality complication of bleeding esophageal varices; (b) toxic substances normally present in the portal blood from the gut now directly enter the general circulation through the collaterals, bypassing the liver, which would otherwise act as a filter. Some of these compounds have effects on the brain that lead to another very serious complication of alcoholic liver disease, namely portal-systemic encephalopathy.

The classic explanation for the production of portal hypertension in alcoholic liver disease is that it results from the mechanical compression of the outflow venous tract of the liver by "expanding, regenerative" nodules. In the liver, blood flows from the portal territory, through a network of vessels called the sinusoids, into the hepatic veins, the outflow system, or post-sinusoidal territory. According to this theory, the obstruction

to blood flow is post-sinusoidal. It is of interest that, until now, there was no real evidence for these nodules' being either "regenerative" or "expanding." Furthermore, this concept confines portal hypertension to cirrhosis (the only stage of ALD where "regenerative" nodules exist) and, by attributing the cause of portal hypertension to a permanent abnormality, also implicitly leads to the assumption that portal hypertension is also irreversible.

Observations by the Biochemical Research and Gastroenterology programs have resulted in the alternative explanation of portal hypertension as being a result of compression of the sinusoid by adematous, enlarged hepatocytes. It has been found that there is striking correlation between hepatocyte surface area and portal pressure. Furthermore, portal hypertension does occur in the absence of "regenerative" nodules, and therefore of cirrhosis. In addition, a substantial number of cirrhotics with "regenerative" nodules do not present portal hypertension. Among cirrhotics, portal pressure is not related to the presence of "regenerative" nodules but to the hypatocyte surface area. Decreases in portal pressure with time coincide with decreases in cell surface area but not with decreases in nodularity; increases of pressure are accompanied by an enlargement of the hepatocytes.

Again, according to the classical explanation of compression of the hepatic veins by "expanding" nodules (post-sinusoidal), there should be an associated widening of the sinusoids, which should be subject to an increased intrasinusoidal pressure. If, on the other hand, portal hypertension is caused by an increase in liver resistance due to enlargement of the hepatocytes that surround the sinusoids, there should be an associated sinusoidal compression. The Gastroenterology group has undertaken a study to determine the site of the resistance resulting in portal hypertension by examining sinusoidal areas in liver biopsies from patients with alcoholic liver disease, patients with non-alcoholic liver disease, and patients with normal livers (non-alcoholics). For each case, the size of the liver cells (hepatocytes) and the sinusoidal calibre were determined by quantitative digital-image analysis using a computerized system. Patients with alcoholic liver disease showed a marked reduction in relative sinusoidal area when compared to non-alcoholic patients with either normal liver histology or with other forms of liver disease. Hepatocyte surface area was significantly increased in patients with alcoholic liver disease when compared with hepatocytes from normal biopsies. Patients with non-alcoholic liver disease had hepatocytes within the normal range. There was a significant inverse correlation between hepatocyte size and sinusoidal area, indicating that larger hepatocytes were associated with sinusoidal compressoin. These data support the hypothesis that hepatocyte expansion and compression of the sinusoidal space appear to be important determinants in the development of portal hypertension in alcoholic liver disease. In addition, the striking difference in the observable sinusoids in alcoholic and non-alcoholic liver disease should provide an added criterion in the histological differentiation of the two conditions.

The methods used to determine portal pressure in patients with liver disease are complicated to perform, invasive, and extremely unpleasant for the patient. Therefore, it is very seldom that they can be repeated on the same individual. The Gastroenterology program has developed a new procedure that consists in introducing a very thin needle (a Chiba needle) into the liver parenchyma and measuring the intrahepatic pressure. This procedure is simple and can be conducted at the bedside; it is performed at the Clinical Institute immediately before obtaining liver biopsies. This technique had been previously correlated with the wedged-hepatic-vein catheterization technique, which is the most commonly used method, and a correlation coefficient of .93 was found between the two measurements. At present there is the possibility of comparing intrahepatic pressure with portal vein pressure during the same procedure. Patients undergoing percutaneous liver biopsy for diagnostic purposes or as part of the PTU protocol were studied. The two measurements were done, one with the needle in the hepatic parenchymatic liver tissue and another after advancing the needle, under X-ray control, into a large portal vein within the liver. After confirmation that the needle was inside the vein (by injection of radio-opaque material), the portal pressure was measured. This procedure offered the possibility of validating the method of intrahepatic pressure measurement by a direct comparison with the portal pressure. The results of this study in 90 patients showed a very close correlation between intrahepatic and portal pressure ($r = .92$).

The therapeutic and conceptual implications of these findings could be very important. The finding that portal hypertension is related to a more functional rather than "permanent" mechanism offers the possibility that, by determining the factors that are responsible for the alcohol-induced increase in cell volume, a treatment might be found for portal hypertension. This treatment, by preventing or reducing the increase in liver cell size, could have a very significant impact on the mortality of alcoholic liver disease by forestalling two of its most serious complications: bleeding from esophageal varices and portal-systemic encephalopathy.

The toxic substances responsible for portal-systemic encephalopathy have not yet been identified. This area has now been studied by the Gastroenterology program in a collaborative project with the Neurology program. The research is described in the Neurology section.

Investigators: L.M. Blendis, Y. Israel, H. Orrego, E.I. Vidins

3. Investigations into the Pathogenesis of Alcoholic Liver Disease, Interaction between Alcohol and Anesthetic Agents, and Genetic Determinants of Hepatomegaly

Most of these studies on the effects of alcohol on the liver have been undertaken in collaboration with the Biochemical Research program. Animals and most human beings do not present liver necrosis even after drinking alcohol chronically for long periods of time. Absence of necrosis might be due to the existence of compensatory mechanisms that increase the availability of oxygen to the liver, thereby protecting that organ from the hypoxia resulting from an alcohol-induced increase in liver oxygen consumption. An obvious possible mechanism is an increase in liver blood flow.

Recently we have begun to study compensatory mechanisms that would deliver an increased amount of oxygen

to the liver following the administration of ethanol and therefore prevent the occurrence of hypoxia-induced necrosis. Previous workers have shown that ethanol administration results in an increase in blood flow to the liver. We have extended these findings by showing that the increase in liver blood flow is due entirely to an increase in portal blood flow. We have further demonstrated that this effect of ethanol requires very low levels of ethanol in the blood, in the order of 3.5 millimoles. (For comparison, in the Highway Traffic Act for Ontario the legal limit of blood alcohol level is equivalent to 17.4 millimoles.) Since the minimum concentration at which the full effect of ethanol on liver blood flow was present corresponds to the Vmax of alcohol dehydrogenase, the possibility arose that this effect is due to ethanol metabolism. We explored this possibility using the inhibitor of alcohol dehydrogenase, 4-methylpyrazole (4-MP), which resulted in the complete inhibition of the effect of ethanol on liver blood flow. These data clearly show that the effect of ethanol increasing splanchnic blood flow is entirely dependent on the metabolism of ethanol via the alcohol dehydrogenase pathway.

It has been claimed that glucagon is released by ethanol. Also, it is known that this hormone increases both the oxygen consumption and the blood flow to the liver. We therefore investigated the role of glucagon in the effect of ethanol on liver blood flow. Our results exclude glucagon from playing a role in the ethanol-induced increase in liver blood flow.

Acetaldehyde, a product of ethanol metabolism, has been shown to produce both vasodilation and vasoconstriction in the splanchnic vascular territory. We therefore analysed the effect of cyanamide, an inhibitor of acetaldehyde dehydrogenase (ACDH), on the ethanol-induced alterations in liver blood flow. The dose of cyanamide (10mg/kg) increased the arterial levels of acetaldehyde following ethanol administration from 3.6 $\pm$ 0.3 to 293 $\pm$ 48 micrometres, while completely abolishing the increase in liver blood flow caused by ethanol administration. In the cyanamide-treated rats given an oral dose of ethanol the percentage of cardiac output delivered to the liver was markedly reduced ($p < .001$). These results present the possibility that a product of ethanol metabolism, namely acetaldehyde, is responsible for a "feedback" effect on splanchnic hemodynamics that would result in an inhibition of the compensatory increase in oxygen delivery to the liver following ethanol administration and therefore in an increase in the potential for hypoxic liver damage. We are now exploring the effects of acetaldehyde, alone and in combination with ethanol, on splanchnic hemodynamics.

While a number of studies show that acute oral administration of ethanol results in increases in liver blood flow, a large body of evidence has also been presented in which such an effect is not observed. To shed light on this discrepancy we have studied, in rats, a number of variables that might modulate or inhibit the effect of ethanol. These included the use of three anesthetic agents studied at two different times after anesthetic administration, and the effect of animal age, gender, and batch and seasonal variation.

Portal blood flows were determined by the radio-labelled microsphere method, in twelve separate experiments in awake rats. Ethanol given at doses ranging from 0.5 to 4.0 g/kg consistently increased portal blood flow by approximately 50% (42.2 $\pm$ 3.5 to 63.4 $\pm$ 6.5 mL/min/kg). The inter-experiment variation was 2.4–3.0%, showing remarkable consistency, typical of an all-or-none effect at the doses employed. On the other hand, the ethanol-induced increase in portal blood flow was completely suppressed by ketamine (75 mg/kg), thiopental (50 mg/kg), and fentanyl (15 μg/kg) when given 15 minutes prior to blood-flow determinations. This suppression was dependent on the dose and duration of anesthesia. The anesthetic agents had no effect on basal hepatic arterial or portal blood flows. Ethanol or the anesthetics were without effects on hepatic artery blood flow. Neither gender, weight (150–350g), nor animal batch had effect on the response to ethanol. Similarly, there was no effect of seasonal variation. The increase in portal blood flow following a dose of 2g/kg of ethanol disappeared only after six hours when blood levels of ethanol had decreased to concentrations below 3 millimoles.

Although there is considerable information available regarding the detrimental effect on the liver of alcohol and of some anesthetic agents, there is little information regarding the effects of anesthetics in alcohol-consuming patients. Not infrequently, emergency operations are performed on patients who have significant blood levels of alcohol. In addition, patients with a history of heavy alcohol consumption with or without recognized hepatic abnormality may also require a general anesthetic at some time.

Anesthetics such as halothane, whose toxic potential is related to hepatic metabolism, would be expected to have more damaging effects following alcohol pre-treatment, particularly in the situation of an increased hypoxic hepatic environment that would shift the metabolism of halothane to a reductive pathway, resulting in the production of increased amounts of reactive intermediates. The increased production of reactive intermediates would be expected to manifest as an increase in conjugated diene levels in the lipid fraction of the liver cell. Also, glutathione, which scavenges reactive intermediates of cellular metabolism, is decreased in the liver of animals treated with acute alcohol; this represents another potential interaction. Such interactions between alcohol and anesthetic agents are the basis of a study that is being undertaken in our laboratory to determine whether prior alcohol consumption is involved in the hepatotoxic effects of anesthetic agents.

We have postulated that when liver damage occurs, it triggers cycles that in combination potentiate each other. Portal hypertension will produce shunts bypassing the liver and decreasing portal blood flow to the liver; also, portal hypertension through gastrointestinal bleeding and hypersplenism can induce anemia. Both situations will reduce oxygen availability to the liver and should increase the risk of hypoxic hepatocellular necrosis in the presence of continued alcohol intake. Also, the presence of collagen in the space of Disse (the space that separates the vascular compartment from the liver cells), with the formation of a continuous basal membrane under the sinusoidal endothelium, can interfere with the optimum exchange of oxygen. Also, liver damage, by increasing acetaldehyde levels in the liver after alcohol intake, can create another vicious circle of increasing severity.

These interactive systems result in a self-fuelled disease requiring ever-lessening degrees of both external precipitating

causes and amounts of alcohol.

We will study the effects of chronic alcohol administration on both hepatocellular necrosis and production of acetaldehyde, using three models of liver damage. Two of these models produce cirrhosis: carbon tetrachloride treatment in phenobarbital-treated rats; and occlusion of the common bile duct using a double ligature technique with excision of a segment of bile duct. Both treatments have been shown to result in liver cirrhosis, which will be graded in severity with histology and liver function tests (transaminases, bilirubin, ascites, ICG clearance). The third model is a special strain of rats obtained from Dr. P. Thibert, Health and Welfare Canada, that present a genetically determined collagenization of the space of Disse.

With these models we plan to analyse the influence of liver damage *per se* on the effects of alcohol, including acetaldehyde production. If positive, these data might also show that liver damage induced by other hepatotoxic factors can also increase the susceptibility to alcohol liver injury. Such a finding could be of importance in circumstances where alcohol abuse coincides with the intake of other potentially hepatotoxic drugs or with infection with viral hepatitis.

Another area of research relates to the genetic determinants of hepatomegaly in rats fed alcohol chronically. Ethanol feeding results in varying degrees of increases in liver weight in the rat. In general, the increase in liver weight above controls has a range that extends from 10 to 60%. In order to determine the cause of this very wide range in magnitude of response, we selectively inbred two groups of rats: (a) those animals presenting maximal hepatomegalies after ethanol (more than 50%) and (b) those presenting minimal hepatomegalies (between 10 and 30%). The inbreeding resulted in two very different types of rats with respect to the response of liver weight to ethanol. In essence, new generations of rats resulting from parents selected for maximal hepatomegalies had an average increase in liver weight after four weeks of alcohol administration of 65% (measured as increase in hepatocyte size), while those selected from animals with small hepatomegalies had an average increase in hepatocyte size of only 25%. We are continuing these studies to determine the nature of this genetic variation. To our knowledge this study might represent the first strong evidence for a genetic component in one of the most frequent and potentially dangerous effects of alcohol in the liver. As mentioned above, our group has suggested that the increase in hepatocyte size might play an important role in the pathogenesis of portal hypertension, one of the most important determinants of mortality in alcoholic liver disease.

Investigators: H.G. Giles, Y. Israel, H. Orrego

NEUROLOGY
Program Manager: P.L. Carlen

The main objective of the Neurology program is to determine the pathophysiological basis of drug-induced encephalopathies so as to be able to develop more rational preventive and treatment strategies. Involving both clinical and animal research, the main areas of concentration are the acute and chronic encephalopathies associated with alcohol abuse. These include acute intoxication, alcohol withdrawal syndromes, chronic alcohol-induced brain damage (dementia, Korsakoff's syndrome, cerebellar ataxia), and portal-systemic encephalopathy secondary to alcohol-induced liver disease. The program also is developing a research line concerned with the enhanced central nervous system (CNS) actions of abused sedative-hypnotic drugs in aged individuals, an important problem considering the recent increase in the aged population in Ontario.

1. The Organic Brain Syndrome and Its Reversibility (Neurological Aspects)

The purpose of this research is to examine the neurological, psychological, and neurobiological concomitants of chronic alcohol abuse in humans. The organic brain syndrome resulting from alcoholism has been shown to be partly reversible in some patients, and these data have generated several hypotheses that are being or will be tested both in the clinic and in the laboratory.

More than 100 recently abstinent alcoholics have been studied in great detail over the past two years. Repeated neurological, psychological, electrophysiological, biochemical, and neuroradiological tests have been performed. Data are being collected in a carefully controlled manner, and preliminary analyses are under way. An ongoing collaboration with Dr. Richard Penn of Rush Presbyterian Hospital in Chicago has been funded by a grant from the the U.S. National Institute on Alcohol Abuse and Alcoholism.

The reversible atrophy noted in previous studies of recently abstinent alcoholics has been substantiated, and its time course is being more carefully elucidated. Cerebral atrophy reversibility has been shown to correlate with clinical neurological measurements of improvement. Cerebral atrophy measures correlate with neuropsychologically measured deficits. However, cerebellar dysfunction in alcoholics has been shown, surprisingly, not to correlate significantly with measurements of cerebellar or cerebral atrophy. The cerebral atrophy measurements and changes in brain density are being quantified by computer. Preliminary data indicate that the brain density increases with prolonged abstinence. Certain electrophysiological abnormalities on computerized EEG have been found that have not been reported previously (for example, alpha frequency is not significantly decreased upon eye opening). All these biological parameters will be correlated with functional measurements.

At present, it is not known whether there are any morphological brain abnormalities in long-term benzodiazepine users and abusers. Some of these patients are now undergoing detailed neurological assessment and CT scan measures. Results will permit a better assessment of the neurotoxicity associated with long-term use of benzodiazepines.

A detailed study of cerebrospinal fluid (CSF) abnormalities in chronic alcoholics is continuing. Previous work has shown a significant CSF acidosis, but no systemic acidosis, in recently abstinent alcoholics. The etiology of this acidosis is being further investigated in human studies and in an animal model, since it could be a causal factor or an important marker of brain damage. Measures of CSF neurotransmitter abnormalities are also under way. Finally, low CSF-ionized calcium has been discovered in chronic alcoholics and could be a significant causative factor for the brain hyperexcitability noted in alcohol withdrawal.

The Neurology program is now considering various treatments of alcoholic dementia based on already published pharmacologic treatments of dementia and recent neurobiological evidence of neurotransmitter deficits noted in chronic organic brain syndromes. These treatments include the administration of cholinergic agonists, adrenergic agonists, and a "nootropic" drug, oxiracetam, with neurobehavioral assessment of the treatment outcome.

Alcoholic brain damage is present overtly in a large percentage of chronic alcoholics; and if one considers the incidence of cerebral atrophy to be a measure of brain damage, then it is present in the majority of them. The implications of alcohol-induced brain dysfunction on society do not have to be stressed. Our finding that the recovery of this brain dysfunction can take anywhere from weeks to months has importance for behavioral intervention strategies, since some alcoholics might not be able to appreciate certain treatments until they recover to the appropriate level. A continuing detailed study of this partially reversible chronic organic brain syndrome also provides further clues to its biological basis. Understanding the biology of the syndrome will ultimately permit the development of more rational treatment strategies.

Investigators: P.L Carlen, L. Fornazzari, B.M. Kapur, C. Waters, D.A. Wilkinson, P.Wu

2. Portal-Systemic Encephalopathy

Hepatic or portal-systemic encephalopathy (PSE) is a very frequent cause of death among patients with alcoholic liver disease. In collaboration with the Gastroenterology program, a human study of alcoholics with PSE is in progress. Clinical neurological, electroencephalographic (EEG), and biochemical measurements are being taken in patients with PSE both when obviously encephalopathic and when in a seemingly normal or almost normal mental state. Using these data, we are defining another population, alcoholic cirrhotics with "subclinical" PSE. Results suggest that certain EEG measurements are sensitive enough to delineate this population. The early identification of alcoholic patients with "subclinical" PSE has important therapeutic and preventive implications.

For more appropriate therapy, the pathophysiology of this syndrome has to be better understood. To this end, we are investigating the possibility that there is a toxic substance in the circulation that is present or altered in PSE patients. In order to

determine the presence of such a substance, ultrafiltrate of serum from PSE patients is infused into the cerebral ventricles of rats. EEG parameters are measured in the infused rats. These parameters are also measured in rats infused with ultrafiltrate of serum (a) of patients with alcoholic liver disease without encephalopathy and (b) of patients who have recoverd from PSE. To test the possibility of an abnormal permeability of the blood-brain barrier as a cause of encephalopathy, rats with normal livers and with carbon-tetrachloride-induced cirrhosis will also be tested to see if liver disease is necessary for the production of encephalopathy. At present, there is evidence of a difference in the EEG parameters of rats infused with encephalopathic serum compared to those infused with control serum.

Understanding the etiology of hepatic encephalopathy is important, as this complication is a very frequent cause of death among patients with alcoholic liver disease. Improved knowledge in this area could result in better forms of treatment.

Investigators: M. Burnham, P.L. Carlen, L. Fornazzari, B.M. Kapur, I. Naquet, H. Orrego, E.I. Vidins

3. Study of Solvent Abuse and the Neurological Complications Resulting from Chronic Solvent Abuse (Glue Sniffing)

Glue sniffing is a relatively common form of drug abuse in the younger and underprivileged population. It can cause serious long-term neurological deficits. In an ongoing investigation, to date over 40 young solvent abusers (mean age 25 years) have been studied in the Clinical Institute. Marked impairment in neurological and neuropsychological test performance was present in the majority of those sampled. Cerebellar symptoms correlated significantly with CT scan measurements of cerebellar and cerebral atrophy, all of which were abnormal in comparison to age-matched controls. CSF biochemical abnormalities were also found.

This study continues to demonstrate that chronic glue sniffing can result in quite significant neurological and neuropsychological dysfunction and cerebellar atrophy. The follow-up study, to see if there is any reversibility of cerebral dysfunction and atrophy with abstinence, is also ongoing.

Investigators: P.L. Carlen, L. Fornazzari, B.M. Kapur, D.A. Wilkinson

4. Cellular Neurophysiological Studies into the Mechanisms of Acute Intoxication and Alcoholic Brain Damage

This research is being conducted in an attempt to understand the basic pathophysiological neuronal mechanisms of acute intoxication, dependence, and brain damage resulting from commonly abused psychoactive drugs. In order to arrive at this understanding, the Neurology program has to date concentrated on two problem areas: (a) the cellular neuronal mechanisms of intoxication, and (b) the neuronal effects of long-term alcohol administration as a parallel to the clinical problem of alcoholic brain damage.

With regard to the first area, by utilizing mainly intracellular electrophysiological recording techniques in mammalian brain tissue slices, we have shown that sedative or mildly intoxicating concentrations of ethanol, pentobarbital, and benzodiazepines — all of which show some degree of cross-tolerance behaviorally — activate an intrinsic neuronal inhibitory mechanism that is a calcium-mediated potassium conductance (Ca-gK). This mechanism involves the opening of potassium channels in the neuronal cell membrane due to a rise in concentration of intracellular free calcium ions. This is a novel finding, for most investigators consider that these commonly abused depressant drugs inhibit central nervous system (CNS) function by activating mechanisms related to gamma-aminobutyric acid (GABA), a major CNS inhibitory neurotransmitter. However, this laboratory has demonstrated that higher, coma-producing doses of these drugs do, in fact, enhance neuronal sensitivity to GABA. Ultimately, treatment strategies might examine drugs that can affect neuronal calcium metabolism rather than concentrating on mechanisms related to GABA.

The neuronal effects of long-term ethanol administration have also been examined with isolated brain-tissue preparations. Recordings from neurons in brain slices from rats chronically exposed to ethanol and then withdrawn for three weeks have shown impairment of the Ca-gK inhibitory mechanism. The working hypothesis is that the Ca-gK is impaired in animals chronically exposed to ethanol because of prolonged raised intracellular free calcium ion concentration that conversely can inhibit Ca-gK as well as cause cell death. Again, if the hypothesis can be generalized to the whole nervous system, one would have to think in terms of a non-GABA-ergic mechanism as one of the major concomitants of alcoholic brain damage/dysfunction.

Drug-withdrawal epilepsy is one of the most common forms of seizure disorder seen in general hospital emergencies in Ontario. There have been very few studies of the pathophysiology of this problem. Slices removed from animals chronically treated with clonzaepam have many epileptiform abnormalities, which increase upon drug withdrawal. This model of acute "dependence" permits us to examine in depth the cellular neuronal mechanisms of tolerance and dependence. Similar experiments with ethanol applied for 2 hours to slices from naive animals have also demonstrated epileptiform activity that can be blocked by raising the perfused calcium concentration, a finding of possible therapeutic significance.

Memory deficits have consistently been demonstrated in human alcoholics. In order to define the cellular mechanisms of memory, hippocampal brain slices from chronically ethanol-fed rats were examined for the degree of long-term potentiation (LTP). LTP is the enhancement of an evoked potential following a train of preceding evoked potentials and is considered a cellular correlate of memory. LTP was impaired in animals exposed to ethanol for several months, compared to pair-fed controls.

A study of the morphology of neurons during and after chronic administration of ethanol was completed in collaboration with Dr. Jean St. Cyr of the Playfair Neuroscience Unit. It is known that some alcoholics show reversibility of cerebral atrophy with maintained abstinence. At the cellular level, the hypothesis was that dendritic regrowth could occur. This has been confirmed by Golgi morphology in rats that were fed ethanol for five months and withdrawn for two months, as

compared to rats fed ethanol for five months and not withdrawn. The fact that morphological regrowth of dendrites has been shown at the cellular level in animals chronically fed ethanol and withdrawn for two months supports a very important concept: that dendritic regrowth is at least possible in adult mammals who have suffered the insult of long-term ethanol administration.

One other abused drug being studied is phencyclidine (PCP), which received much public attention because of the bizarre behavior it induces in human abusers. It is also a relatively common additive to other abused substances such as marijuana. PCP was initially used as a general anesthetic. Its use was discontinued after it was discovered that during the recovery from anesthesia, human patients would become hyperexcited and sometimes convulse. The acute effects of PCP, which is known to cause central nervous system excitation as well as inhibition, have been studied further in the in-vitro hippocampal slice preparation. PCP has shown a dose dependency in single neuronal recordings; the lower doses cause neuronal excitation and the higher doses cause anesthesia. The membrane mechanism of action of this drug is now being examined by intracellular recording techniques. Data suggest that PCP impairs ionic fluxes to both sodium and potassium ions.

In summary, by understanding the cellular neuronal mechanism of action of commonly abused psychoactive drugs, we can then more rationally develop future treatment strategies. If the hypothesis that neuronal calcium metabolism is much more important than GABA-ergic mechanisms in the cause of acute intoxication, drug-withdrawal symptomatology, and long-term drug-induced brain damage, then future therapeutic interventions will have to take these data into account. For example, calcium-blocking drugs are in wide use for the treatment of cardiac disease, and there have been some preliminary reports that these drugs can prevent brain damage in acute neurological emergencies. There may even be a role for similar kinds of drugs in the treatment of neuronal dysfunction due to other commonly abused CNS-depressant drugs. This role, however, is quite hypothetical at present.

Investigators: T. Blaxter, P.L. Carlen, M.F. Davies, I. Naquet, P. Wu

5. Drugs and Aging

There is a significant problem of sedative-drug and alcohol overuse and abuse in the aged population. It is well known that older persons have less tolerance to the intoxicating effects of alcohol and other sedative drugs, and also can have idiosyncratic reactions to these drugs (e.g., excitation). The Neurology program is undertaking both clinical and laboratory studies of this problem. A psychophysiological laboratory is being established in the Clinical Institute to study the neurobehavioral effects of acutely administered alcohol in different age groups. In the laboratory, data have already been generated showing that ethanol at relatively low doses (20 millimoles) has *inhibitory* actions on neurons from younger mature rats and *disinhibitory* actions on older neurons. Such studies will help provide a more rational basis for the management of sedative-hypnotic drug and alcohol use in the elderly.

Investigators: A. Baskys, P.L. Carlen, M.F. Davies, L. Fornazzari, C. Niesen, D. Riley, C. Waters

PSYCHIATRY
Program Manager: F.B. Glaser

Although there has been a Department of Psychiatry in the Clinical Institute since its inception, and although members of the department have participated as both principal investigators and collaborators in various research projects, the program as such was not given a research mandate until 1983. At that time research goals were approved that involved the exploration of, on the one hand, psychiatric problems and their treatment and, on the other hand, alcohol and drug problems and their treatment. Basically, the questions asked are: To what degree do difficulties of a psychiatric nature contribute to the development of alcohol and drug problems? What are the effects of psychiatric treatment methods upon persons with alcohol and drug problems?

The Psychiatry program has undertaken research in three areas: the development of alcohol and drug problems in professional populations; the epidemiology of psychiatric disorders in patients with alcohol and drug problems; and the treatment of alcohol problems through an integrated pharmacological-psychological approach. Each line of research has received grant support from external agencies. Since the last *Research Digest*, considerable progress has taken place in various projects in all three lines.

1. The Development of Alcohol and Drug Problems in a Professional Population

The background to the study of substance abuse problems among physicians has been described in *Research Digest 1982–84*. In brief, in 1977 an opportunity arose for the investigation of physicians with alcohol and drug problems when, under the leadership of the College of Physicians and Surgeons of Ontario, the Clinical Institute was asked to participate in a consortium of agencies whose goal was to set up a comprehensive program of research, education, and treatment in this area. By midyear, physicians seeking treatment were being comprehensively evaluated in the Assessment Unit prior to treatment. Because uniform measures were obtained on other Clinical Institute clients, comparisons were faciliated. A sample of 36 physicans was collected over a three-year period, and subsequently an extensive analysis of the data was carried out.

There have been several interesting findings from this body of data. Physicians with alcohol and drug problems were found to resemble (in the aggregate) other Ontario physicians in many respects. However, some differences were found: the Clinical Institute physician clients were more likely to be between 46 and 55 years of age, were more likely to be separated or divorced, and were more likely to be in solo practice than were other Ontario physicians. Further research is needed to investigate whether these differences are related to the development of drug problems. It was also found that, on many measures, physicians with alcohol and other drug problems closely resemble other non-medical professionals, as well as business executives and managers, with alcohol and other drug problems; however, all three groups are significantly different from other non-professional persons with alcohol and drug problems.

A potentially significant finding was that there were differences in the distributions of personality patterns among the physicians and other groups of clients. So that this finding might be understood, the personalities of 1,000 randomly selected Ontario physicians were studied through a mailed survey. As an effective response rate of 83% was achieved in this survey, the results can be said to be representative of Ontario physicians. When comparisons were made, the physicians with alcohol and other drug problems scored significantly higher than all Ontario physicians on several scales of the Basic Personality Inventory, particularly those measuring depression, anxiety, social introversion, and impulse expression. Future research should consider the possibility of the interaction of personal characteristics with social and professional factors in the etiology of drug problems.

In the study of Ontario physician personality, respondents were also asked whether they had ever been treated for problems with alcohol and other drugs. A review of the literature on the prevalence of drug problems among physicians revealed that the proportion of physicians who have such problems is unknown. Thus, our finding that the population of Ontario physicians who have been treated (1.2%) is similar to that found in population studies is significant, especially in light of widespread statements that physicians are particularly likely to suffer from drug problems. A more detailed study of the prevalence of drug problems among physicians and other health professionals is clearly needed.

In approaching another aspect of this complex problem, the program is obtaining descriptive data on a unique treatment initiative. A group of Physician Advocates has been formed to provide support and encouragement to other physicians having alcohol and drug problems. The Advocates are initially intended to provide their fellow physicians with assistance in re-entering the community and the practice of medicine following their treatment; in time they will also become active in identifying untreated physicians with problems and in facilitating their entry into treatment. Such a self-help program is unique in terms of the treatment of physicians, but bears many similarities to self-help programs that have become so significant a part of treatment in many areas, particularly that of alcohol and drug problems (e.g., Alcoholics Anonymous, drug-free therapeutic communities).

Other initiatives have been undertaken in this line of research as well. Of potentially great significance is the development of a unique computerized bibliography of the area's vast and unruly literature. With data-base methodology it will become possible to access all information by several hundred variables (as well as permutations and combinations of these variables) throughout the whole of the literature. When developed, this should prove a major boon to all researchers in the field, as well as markedly facilitating this program's efforts.

Within the last two years, representatives of the professions of medicine, dentistry, nursing, pharmacy, and veterinary medicine have come together to form the Ontario Health Professionals Assistance Program to help members of their professions who have problems with alcohol and other drugs. This interdisciplinary group will provide a vehicle through which the five professions can cooperate in the sharing of information,

education and training, assessment and referral of professionals with problems, and research. With the support of the licensing bodies and professional associations of five major health professions in a large jurisdiction, this organization may be unique in the world. The possibility of the collection of uniform data on members of all five professions presents an opportunity to carry out research making comparisons among the professions and to study the possible role of professional factors in the development of drug problems among other health professionals in addition to physicians.

Investigators: J.M. Brewster, F.B. Glaser

2. The Epidemiology of Psychiatric Disorders in Patients with Alcohol and Drug Problems

Clinical experience within this program and elsewhere suggests that the entire spectrum of psychiatric disorders may be seen in patients with alcohol and drug problems. These disorders may play a causative role in the substance abuse; they may be a result of the use of alcohol or drugs; or they may occur concurrently with, but be independent from, the substance-use disorder. Where psychiatric disorders occur, it is of obvious importance not only to detect them but to understand their relationship to the excessive use of alcohol or drugs. Treatment strategies, as well as the eventual prognosis, will vary accordingly.

A particular problem has been the diagnosis of depression in patients with alcohol and drug problems, since the direct effects of alcohol, opiates, and other drugs, as well as their withdrawal syndromes, often produce symptoms that resemble depression. Differentiation between significant psychogenic mood disorders and those secondary to substance abuse may be crucial in treatment planning. The inaccurate assessment of mood in our patient population can on the one hand lead to the inappropriate use of antidepressant medication in a population already in difficulty with the use of substances, and on the other hand to failure to deal with a potentially treatable affective disturbance.

Sex differences in the prevalence of psychiatric disorders in alcohol and drug populations have not been extensively studied, a fact that reflects the general paucity of data on sex differences in this field. Previous studies have suggested higher rates of affective disorders among females and higher rates of antisocial personality disorders among males in these populations. Since the treatment implications of such diagnoses are widely divergent, knowledge of the existence and extent of sex differences will have an important bearing upon treatment planning.

For the most part, no systematic attempt is made to evaluate the possibility of psychiatric disorder in patients who present themselves for the treatment of alcohol and drug problems at non-psychiatric facilities. This lack is unfortunate in the light of one recent study's findings that as many as 20% of all admissions to such facilities may require that the psychiatry service be active in following and maintaining control of the patient. Referrals on clinical grounds by treatment personnel tend to be of disturbing, rather than disturbed, patients. The role of the psychiatrist in such a case is as a nuisance eliminator, rather than as a diagnostician or a therapist.

The Psychiatry department has for some time been exploring one possible approach to the screening of treatment applicants for mental disorders. Goldberg's General Health Questionnaire (GHQ), a simple self-administered screening instrument, has been widely used in community settings throughout the world, and has usually exhibited satisfactory levels of sensitivity and specificity when validated against clinical psychiatric interviews. To date, the GHQ has not been validated specifically for use within alcohol and drug treatment populations. Preliminary use of the instrument in a large sample of Clinical Institute clients suggested that it may prove to be useful.

Such a validation study has now been carried out by the Psychiatry department as part of an investigation into the prevalence of psychiatric disorders and related sex differences in an alcohol and drug population. The goals of this research project have been threefold: (a) to provide a valid estimate of the extent and types of psychiatric disorders in the Clinical Institute admission population; (b) to indicate whether, in this population, there are systematic differences between males and females with respect to the prevalence of specific psychiatric disorders; and (c) to tell us whether the GHQ is a sensitive and specific indicator of psychiatric disorder in our population.

A sample of patients registering at the Clinical Institute over a one-year period was studied. The 503 patients, half of whom were females, were given a standardized, highly structured interview, the Diagnostic Interview Schedule (DIS), developed for community use by investigators working under the aegis of the National Insititute of Mental Health in the United States. At the same time, patients also completed the General Health Questionnaire and standardized depression inventories, as well as self-rating measures of alcohol and drug consumption.

The DIS is sufficiently structured and specific that it can be utilized effectively by lay interviewers, something that not only facilitated this study but may lead to wider application of both the findings and the techniques employed in future. Once completed, the data contained in the interview are translated into psychiatric diagnoses (or the absence thereof) by an appropriate computer program. Thus, the process of diagnosis can be completed without the direct involvement of a psychiatrist, a factor that will facilitate more general applications.

Data analysis is under way and should yield many interesting results. Preliminary findings on the first 337 patients to enter the study indicate that three-fifths of the sample had a current psychiatric disorder in addition to their alcohol or drug problem. The most widespread psychiatric problems in this sample included antisocial personality disorder, anxiety disorders (particularly phobias and generalized anxiety), psychosexual dysfunctions, and depressive disorders. Male patients were more likely to have antisocial personality disorder, whereas psychosexual dysfunctions, phobias, panic disorder, obsessive compulsive disorder, bulimia, and mania were found more often among female patients. If traditional cutoff scores are used, the GHQ correctly classified 70% of the patients in the sample. The sensitivity was high; that is, most psychiatric cases were picked up by the GHQ. However, a large number of false positives were also identified. Work is proceeding on determining the best way to use the GHQ in this population.

Information generated by this large study should lead to greatly improved planning and execution of psychiatric services

for the Clinical Institute population and, by generalization, other populations seeing treatment for alcohol and drug problems in Ontario and elsewhere. Finally, the study may be utilized to focus further research in this program by directing it toward those psychiatric disorders that are most prevalent in our population.

Investigators: F.B. Glaser, H.E. Ross

3. The Treatment of Alcohol Problems through an Integrated Pharmacological-Psychological Approach

Drugs are often used in the treatment of alcohol-related problems with the expectation of reducing alcohol consumption. One strategy is the use of an alcohol-sensitizing drug, such as disulfiram (Antabuse) or citrated calcium carbimide (Temposil). Disulfiram has been used in treatment since 1948. However, recent clinical reports suggest that its long-term use may be associated with appreciable toxicity. Further, there is no evidence that disulfiram is effective in reducing alcohol consumption past three months.

Calcium carbimide is used less often than disulfiram in alcoholism treatment for two principal reasons. First, the efficacy of calcium carbimide in reducing alcohol consumption has not been established. Second, there has been a widespread but unverified belief that it fails to exert significant anti-alcohol protection. This belief seems to be related to its short duration of action, which requires that the medication be taken twice daily for continuous protection. However, its short duration of action may well permit calcium carbimide to be used in an innovative manner, and in combination with other methods of treatment.

The relapse prevention treatment model based on Bandura's theory of self-efficacy, developed in the Clinical Institute, involves the painstaking specification of situations in which relapse to drinking is highly likely; the design and teaching of self-regulatory and social skills that represent alternative coping strategies in these specific situations; and the assignment of "homework" tasks in the patient's actual environment that provide success experiences and gradually increase the patient's perception of his or her ability to negotiate high-risk drinking situations successfully.

The ongoing study, in collaboration with Health Care Systems Research, examines whether an alcohol-sensitizing drug (calcium carbimide) might not be utilized as a critical element in the psychosocial intervention process. During counselling sessions, clients learn to take the drug in anticipation of high-risk situations for relapse. As treatment proceeds, they are encouraged to use the drug with decreasing frequency and to substitute for it alternative non-drug coping devices. Thus, calcium carbimide becomes a critical element within the context of an overall psychosocial intervention strategy, rather than a treatment in itself.

There are two goals in this research: first, to establish the efficacy of calcium carbimide in reducing alcohol consumption, and to specify the frequency, characteristics, and determinants of toxicity associated with its repeated administration (Study #1); and second, to test the value of self-efficacy therapy combined with calcium carbimide alone in a randomized controlled trial (Study #2). In addition, the predictive value of patients' initial outcome and efficacy expectations with regard to the actual outcome of treatment will be examined.

Study #1. The first study is a double-blind placebo-controlled single-crossover experiment. After an initial assessment period of five to seven days, patients who have chronic and severe alcohol problems, who have abstinence as their primary treatment goal, and who are agreeable to using calcium carbimide to attain this goal are randomly assigned (with their informed consent) to one of the two outpatient treatment conditions: (a) calcium carbimide 50 mg twice daily, or (b) placebo twice daily. After two months of treatment, each patient is switched to the alternative treatment condition for an additional two-month period. All patients receive both medical and psychosocial treatment.

The assessment procedures include patients' self-reports: of their use of the medications; of their daily mood states; and of their craving to use alcohol. In addition, daily urine samples mailed to the clinic are analysed for the presence of alcohol and a tablet marker as objective tests of compliance. Treatment success (or failure) is determined in terms of the record of compliance with the requirements of the study, in terms of their drinking, and in terms of any adverse drug reactions.

Study #2. The second study features a randomized control-group design in which patients who have satisfactorily completed the first study are assigned to one of two treatment conditions. In one, the treatment is calcium carbimide only, taken on an "as needed" basis. In the other, calcium carbimide is used in the same manner, but is combined with self-efficacy therapy. Both groups have regular appointments with their physician for the duration of the study. We hope to have at least 36 patients complete Study #2. These patients will have participated in Study #1 and will have remained abstinent for the first four-month period. Following completion of Study #2, the patients will be closely followed for an additional ten-month period, and at six-month intervals for an additional two years.

Our patient recruitment for the study was completed in February 1986. A total of 130 patients were assessed and started on the treatment. Of these, we expect that about 70 patients will complete Study #1, and that at least 36 of these patients will complete the entire 14 months.

Our initial observations of patients' responses to the treatment are encouraging. A study of the 36 patients who were in treatment from January 1984 to December 1984 was conducted. The patients' compliance to submit daily urine samples and to make daily report of their drinking was 93% and 95% respectively. We found, on the basis of urine testing, that 26 (or 77%) of the patients drank on at least one occasion; half of these patients denied drinking in their daily reports. Most of these patients, however, drank on only one occasion, and their drinking did not result in adverse alcohol reactions. Systematic testing for patients' drinking provided valuable information for making clinical decisions regarding patient management. Overall, drinking was detected by the alcohol monitoring test on only 89 occasions (or 1.9% of the total of 4,696 treatment days). Similarly, compliance to take the medications has been systematically monitored on a daily basis for all patients. Although we have not yet analysed these data, our impression is that patients comply with the treatment conditions by taking

their medications on a regular basis during the first four months of treatment (Study #1), and thereafter intermittently as needed.

Persons with alcohol problems often find it most difficult to abstain from drinking during the first four months of treatment. Study #1 will provide new and important information on the efficacy of calcium carbimide in assisting patients to negotiate this critical period. In addition, the toxicity of the drug will be further explored. Study #2 will explore the efficacy of a novel and integrated pharmacological-psychological approach. It will also provide an initial exploration of the concepts of outcome expectations and efficacy expectations in the treatment of chronic alcohol-related problems. It is hoped that this new integrated approach to treatment will offer a significant treatment advantage to some patients. Beyond this, its success will indicate the potential value of other possible combinations of pharmacological and psychological treatments.

Investigators: H.M. Annis, J.E. Peachey

BIOCHEMICAL RESEARCH
Program Manager: Yedy Israel

Research in this program continues into two general areas of inquiry:

1. To study the mechanisms underlying alcoholic liver disease in order to provide a knowledge base for treatment;
2. To develop simple indicators or a battery of indicators to detect the continuous use and pattern of consumption of ethanol in hazardous amounts.

The two research areas are directly related to the Foundation's aims of increasing knowledge needed for developing methods of preventing or ameliorating chronic physical and behavioral consequences related to the excessive use of alcohol. The first area is of importance in that about 25% to 30% of the excess mortality rate in alcoholics is due to alcohol-induced liver disease. Understanding the mechanisms of this drug-induced damage will lead to improved treatments. The second area is of special relevance because a large number of studies have demonstrated that those who undergo treatment at an early stage of their alcoholism have very much better chances of recovery than those treated in later stages of the disease. This research is therefore an antecedent to prevention.

1. Studies on the Effects of Alcohol in the Liver

Death related to alcoholic liver disease has two predominant causes: (a) cell necrosis with a reduction of functional effective liver mass, and (b) portal hypertension.

In the study of the biochemical mechanisms of alcohol-induced liver disease, effective linkages have been forged with the Gastroenterology program that permit the transfer of basic research into the clinical environment. In addition, there is effective collaboration in some of the basic research projects.

Propylthiouracil and Hypermetabolic State. Earlier studies by our program have demonstrated that both acute and chronic alcohol consumption lead to a hepatic hypermetabolic state characterized by increased rates of ethanol metabolism and by an elevated consumption of oxygen. The latter has been shown to result in an accentuation of the hypoxic state in the centrilobular zone of the liver, which renders the liver more susceptible to hypoxic necrosis. The above findings, now confirmed in a number of centres, led to the hypothesis that antithyroid drugs such as propylthiouracil (PTU), which abolish the hypermetabolic state, could prevent hypoxic liver damage. In present studies we have investigated the conditions that lead to the expression of the hypermetabolic state and the mechanism by which PTU prevents it. We have found that a sustained high intake of alcohol, as induced in young growing rats administered ethanol in liquid diets, is required for the hypermetabolic state to occur. We further found that PTU can block metabolic tolerance induced by chronic administration of alcohol in conditions in which alcohol dehydrogenase levels are increased, while not affecting the microsomal ethanol-oxidizing system. On the other hand PTU blocked the increases in the rate of hepatic oxygen consumption. These studies strongly suggest that PTU inhibits the metabolism of ethanol by reducing the rate at which the liver can utilize oxygen (and thus oxidize NADH). The implication for clinical studies is that the rates of ethanol metabolism could be used as an indicator to titrate the dose of PTU required during treatment. The rates of alcohol metabolism are also likely to predict who is most likely to benefit from PTU therapy. Since alcoholics metabolizing ethanol present higher plasma acetate levels than controls, these levels could constitute a good indicator of hepatic hypermetabolic state and of PTU effects. Present methods available for determination of plasma acetate are cumbersome and lengthy. We have developed a simple and rapid methodology to determine acetate levels, in which plasma is mixed with methanol and sulphuric acid leading to the quantitative formation of methylacetate, which is determined by head space gas chromatography.

Investigators: G. Giles, Y. Israel

Glutathione and Alcohol Liver Injury. Liver-cell death in alcoholic liver disease occurs predominantly in the centrilobular (periacinar) areas of the liver that (a) are exposed to low oxygen tensions and (b) are most active in transforming some substances into toxic electrophiles. Glutathione (GSH), which is known to protect against these toxic substances, is lowest in the centrilobular zone. Acute administration of ethanol leads to a marked reduction in hepatic GSH levels. We have investigated the metabolism of liver GSH depletion induced by acute ethanol and the possible compensatory mechanisms for GSH repletion following chronic alcohol administration. Studies investigating the acute effects of ethanol on ^{35}S-glutathione turnover indicated a greater utilization or loss of hepatic GSH following ethanol administration. We demonstrated that the liver of ethanol-treated animals actually loses its GSH into the circulation. GSH efflux from the liver into the hepatic vein could explain in a quantitative manner the loss of hepatic GSH.

We found that in the rat, compensatory mechanisms develop upon chronic alcohol treatment such that GSH levels are not decreased but are actually increased. In human alcoholics who develop alcoholic liver disease, the compensatory mechanism or mechanisms appear deficient, in that markedly reduced hepatic GSH levels are found. Thus, understanding the nature of the compensatory mechanisms is of potential importance. We postulated that, following chronic alcohol treatment, compensatory mechanisms are induced to increase the availability of GSH precursors to the liver. In support of this hypothesis, we found that the enzyme gammaglutamyl transpeptidase (GGT), which is elevated in the liver of alcohol-fed animals, is expressed as an ectoenzyme facing the sinusoidal (blood) space. This enzyme is able to hydrolyse circulating GSH into GSH precursor amino acids, which, unlike the intact molecule of GSH, can cross the liver cell membrane. The livers of animals fed alcohol chronically were shown to utilize 100% more circulating GSH than those of control animals, and such an effect correlated highly ($r = .95$) with hepatic GGT levels. Thus, plasma GGT, used as an indicator of chronic alcohol consumption, may actually represent a hepatic compensatory mechanism to replenish the liver with GSH

precursors. These studies open the possibility of investigating in clinical populations the role of this compensatory mechanism.

Investigators: Y. Israel, H. Orrego, H. Speisky

Biochemical Mechanisms of Control of Hepatocyte Volume. We have previously shown in a number of rat strains that chronic administration of ethanol results in enlargement of liver cells. This is predominantly due to the accumulation of intracellular water, which leads to a marked compression of the extracellular space. It was postulated that this compression occurs because the extracellular sinusoidal and blood spaces (pathways) impose a lower resistance to hepatocyte expansion than the capsule surrounding the liver. Portal hypertension was proposed to be produced by the compression in the extracellular space. Extension of these concepts into the clinic (see Gastroenterology program) has shown that sinusoidal calibre is dramatically reduced (80%) in alcoholics and that hepatocyte size correlates well with portal pressure ($r = .7–.8$).

In recent studies the biochemical mechanisms that control intracellular water accumulation and hepatocyte volume were investigated. We hypothesized that the proton load of the strongly ionized acetic acid, produced intracellularly during the metabolism of alcohol, stimulates the H^+/Na^+ antiport. Stimulation of the antiport is known to lead to H^+ extrusion from the cell in exchange for extracellular Na^+ and to result in intracellular accumulation of water. As of the writing of this report, the following findings have been obtained: (a) isolated hepatocytes can be induced to expand in conditions that lead to intracellular accumulation of acetate; (b) volume expansion above is blocked by amiloride, an inhibitor (clinically available) of the H^+/Na^+ antiport; (c) ethanol-induced hepatocyte expansion is fully blocked by pyrazole, an inhibitor of alcohol dehydrogenase. Therefore, present studies suggest that it may be possible to reduce hepatocyte expansion (and portal hypertension) induced by alcohol.

Investigators: Y. Israel, H. Orrego, D. Stewart

2. Markers of Alcohol Consumption

Alcohol Dipstick. Studies previously reported by us led to the development of a reliable and sensitive method to determine alcohol in biological fluids, in the form of a dipstick or reagent-strip. Color developed in 60 seconds is proportional to the concentration of ethanol. In previous studies, in which serum or urine alcohol levels were determined by laboratory staff by the new dipstick methodology and by gas chromatography, correlation coefficients of $r = .90$ were achieved when the alcohol levels obtained by the two methods were compared. In recent studies the dipstick was tested in a clinical setting by clinical staff not trained in analytical procedures. Patients on the anti-alcohol drug calcium carbimide were asked to submit urine samples for testing. All positive samples and every twentieth negative sample analysed by the dipstick method were sent to the laboratory for testing for alcohol by an enzymatic spectrophotometric method. In the total of 4,370 urine samples, analyses by the two methods showed a correlation coefficient of $r = .96$. This constitutes the first demonstration of successful transfer to the clinic of the dipstick methodology.

Investigators: Y. Israel, B. Kapur, J. Peachey

Immune Response to Acetaldehyde-Protein Adducts. Production of Monoclonal and Polyclonal Antibodies That React with Acetaldehyde-Containing Epitopes. This is an area in which we have recently made advances with implications for our research on both markers of chronic alcohol consumption and pathogenesis of alcoholic liver injury. A number of studies have indicated that acetaldehyde, a product of alcohol metabolism, in concentrations present in blood of alcoholics consuming alcohol (20–100 micromoles) can bind to amino acid residues in proteins, including hemoglobin and albumin. Binding is, however, so limited that it has not been possible to determine changes in proteins at these levels of acetaldehyde unless radioactive acetaldehyde is used. We hypothesized that acetaldehyde binding to proteins would convert the amino acid residues into haptenes, which would be recognized as foreign by the immune system. Serums of animals immunized with hemoglobin bound to acetaldehyde showed immunoreactivity towards hemoglobin-acetaldehyde but less immunoreactivity to hemoglobin control. This finding suggested that immunoglobulins in the polyclonal serum react with acetaldehyde-containing epitope(s). We proceeded to select B-lymphocytes that produce the latter immunoglobulins. Spleen cells of animals immunized with hemoglobin-acetaldehyde conjugates were hybridized with tumor cells (myeloma) to both transfer the DNA immunoglobulin information to the myeloma and allow resulting hybrids to grow in cell culture. Of 420 hybridoma clones, 16 clones produced immunoglobulins that reacted with higher affinity against hemoglobin-acetaldehyde than with hemoglobin control; four of these presented over 50 times greater reactivity for hemoglobin acetaldehyde than for hemoglobin control. It was further found that when the immunoglobulins produced by these clones were tested against albumin-acetaldehyde adducts, a strong immunoreactivity was obtained, which was not seen for control albumin, thus showing that the immunoglobulins react with small epitopes containing the acetaldehyde moiety and are therefore independent of protein structure. These studies were followed by the immunization of mice with a non-mammalian protein (KLH) coupled to acetaldehyde (KCH-Ach). Polyclonal serums of KLH-Ach-immunized animals show immunoreactivity to mammalian proteins if the latter have been modified by acetaldehyde, but do not react with unmodified proteins. Hemoglobin modified by acetaldehyde at concentrations present in the blood of alcoholics consuming ethanol (20–100 micromoles) was clearly identified from control hemoglobin by polyclonal serums prepared both from mice and from rabbits. Further studies indicated that the polyclonal antibodies recognize the acetaldehyde moiety bound to synthetic polylysine-acetaldehyde adducts. Present studies are addressing the determination of acetaldehyde-modified hemoglobin by radioimmunoassay in blood of alcoholics, as a test of chronic alcohol consumption. The rationale for these studies using hemoglobin, a long-half-life protein (approximately 120 days), parallels that of the use of glycosylated hemoglobin as an

indicator of mean plasma glucose levels over prolonged periods in diabetic patients.

The studies above suggested that acetaldehyde-conjugated proteins formed *in vivo* upon chronic alcohol consumption would become neoantigens generating an immune response against the acetaldehyde-containing epitopes. This was indeed found to be the case. Mice fed alcohol for 45 to 50 days developed antibodies that recognized acetaldehyde-modified proteins.

In addition to the use of antibodies in the diagnosis of excessive chronic alcohol consumption, the implication of these findings for alcoholic liver disease stems from the fact that acetaldehyde-modified proteins formed in the surface of hepatocytes can lead to specific immunoglobulin and complement attachment to the cell membrane. Such a concerted reaction is known to produce cell swelling and lysis and thus it may constitute an added mechanism of hepatocyte ballooning and necrosis in alcoholics. We are currently investigating the existence of immunoglobulins specific for acetaldehyde-epitopes in the serum of patients with different degrees of alcoholic liver disease and with different histopathological manifestations. Data obtained indicate that immunoglobulins against acetaldehyde-epitopes are markedly elevated in patients with alcoholic hepatitis.

Investigators: Y. Israel, O. Niemela, H. Orrego

Presence of Acetaldehyde Condensates in Urine: Animal and Human Studies. As indicated above, acetaldehyde binds to a number of proteins. We hypothesized that upon degradation of these proteins, products containing the acetaldehyde moiety would appear in the urine. These would constitute specific markers of alcohol consumption. This hypothesis was tested by the labelling of rat red cells with acetaldehyde double-labelled in carbon-1, both the ^{14}C and ^{3}H(CH_3–^{14}C–^{3}H–O). These red cells were re-injected into the bloodstream of the same animal. Urine of these animals separated by TLH and HPLC presented radioactive peaks that contained either the ^{14}C label or the ^{3}H label. In addition, a specific peak contained both ^{14}C and ^{3}H in a ratio identical to that in the ^{14}C/^{3}H-labelled acetaldehyde originally used to label the red cells. Such a peak, putatively containing the intact ethenyl group of acetaldehyde (CH_3–^{14}C–^{3}H–R) with a biological half-life of approximately seven days, has a molecular weight of approximately 1,200, and presents ultraviolet absorption characteristics typical of a small peptide. The presence of such a compound (or compounds), tentatively termed alcohol-specific product or ASP, was investigated in the urine of seven alcoholics recently admitted to the Addiction Research Foundation and of seven controls. ASP was found in the seven alcoholics but not in five of the control subjects. The other two control subjects presented ASP peaks, but substantially smaller than those found in the alcoholics. Present studies are investigating rapid methodologies for the detection of ASP in large populations, which will be followed by complete kinetic studies of ASP disappearance from urine upon hospitalization, in order to validate its use as a marker of chronic alcohol consumption.

Investigators: P. Devenyi, Y. Israel, B. Tang, D.W. Teller

Skin Alcohol Elimination: Development of a "Skinalyzer" to Determine Blood Ethanol Concentrations. It has been known for over fifty years that a minor fraction (about 1%) of ethanol elimination can be accounted for by evaporation from the skin. The possibility of non-invasively estimating blood ethanol levels from ethanol vapor above the skin would open a number of scientific, medical, and legal options not available at present.

Starting with the premise that skin would, like the lung, allow ethanol to evaporate from its exposed surface, we hypothesized that a system to detect minute amounts of ethanol vapor above the skin would allow the determination of blood or plasma ethanol levels. We found that a minute sensor (1 × 0.5 cm) used in fire alarm systems, the Figaro sensor, responded well to ethanol vapor equilibrated with solutions containing alcohol in the pharmacological or toxicological range. The Figaro sensor responds with an electric signal to combustible gases (carbon monoxide being one) in contact with a transducer to which an electric current has been applied. No combustible gases are excreted in measurable amounts from the skin of humans or animals who have not consumed ethanol. The sensor was built with the support of the Foundation's Human Responses Laboratory into a system with digital display calibrated in mg/dL of ethanol. The instrument ("Skinalyzer" was shown to have utility in determining ethanol vapor above biological fluids with r values of .99 when compared to gas chromatography. Further, it was shown that it could be effectively used to determine plasma ethanol levels from ethanol vapor above the skin in humans, rabbits, and rats ($r = 0.96$). Rates of blood ethanol elimination for these species were virtually identical whether calculated further to blood sampling followed by gas chromatographic analysis or by the use of the "Skinalyzer" method, in which the small probe is placed over the skin for 30 seconds.

The instrument is self-contained, and some additional units are being built for on-site testing at different clinical settings in various countries. We are also exploring the miniaturization of this system with microchip sensors for use in a form like a wristwatch.

Investigators: G. Giles, Y. Israel

Alcohol Abuse Identification Battery. We have just completed a five-year program with Health Care Systems Research in which the predictive ability of a series of putative indicators of chronic alcohol consumption — biochemical, medical, and psychosocial — was investigated. The best biochemical indicators of the large number tested were gammglutamyl transpeptidase (GGT) and mean corpuscular volume (MCV). These indicators had low sensitivities (20–35% of alcoholics had elevated values) to identify alcoholic populations from controls. However, when they were altered they had good specificities (90% of controls had normal levels). A combination of medical indicators and of trauma provided sensitivities up to 80–90% but were less specific and more laborious. Data indicated that there is much need for a simple, specific, and sensitive indicator of chronic alcohol consumption, for use in early identification of excessive alcohol consumption and in monitoring treatment outcome (see studies above).

Investigators: S. Holt, Y. Israel, H. Skinner

SOCIOBEHAVIORAL RESEARCH
Program Manager: D.A. Wilkinson

The overall purpose of the Sociobehavioral Research program is to address issues in the field of alcoholism and drug abuse using the conceptual and methodological approaches associated mainly with the discipline of psychology. Project lines can be grouped into four closely interrelated areas that bear on particular stated goals of the Foundation. These four areas of research are as follows:

1. Behavioral processes in drug dependence;
2. Assessment of drug-dependent persons;
3. Treatment of drug-dependent persons;
4. Influence of systems on drug dependence and drug use.

The preponderance of effort in the program is devoted to work on assessment and treatment, and hence mainly involves human subjects. A smaller proportion of effort is devoted to laboratory studies (some involving animals) and research on systems, which tends to involve further analysis of large sets of data accessible to the public. It is important to emphasize that individual investigators are usually active in more than one of the above areas, and may identify themselves primarily with research on a particular substance (e.g., tobacco) or population (e.g., multiple drug users). Moreover, most of the research in the department involves collaboration with persons in other departments or divisions or other institutions. Thus, the delineation of the four areas represents a coherent framework for describing the research functions of the department as a whole, but not for categorizing its members.

Intellectually, the cohesion in this program is the emphasis on the study of social and behavioral aspects of drug-abuse problems. For example, neuropsychology research is closely integrated with the Neurology program in an effort to characterize relationships between measurable features of neural tissue and measurable features of performance. Although both activities are critical to an understanding of cognitive deficits in alcoholism, the primary contribution of the Sociobehavioral Research program is to characterize deficits in behavior. Similarly, although other programs have an interest in tolerance and dependence, their emphasis is on a neurochemical approach, whereas in this program the focus is on conditioning and learning. The Temposil study involves the collaboration of sociobehavioral with psychiatry research, and the crucial contribution of sociobehavioral research is in the integration of behavioral treatment methods with a pharmacological treatment that is being gradually withdrawn. Such differences in approach provide an important and valuable diversity in leading to the understanding and treatment of drug and alcohol problems.

1. Behavioral Processes in Drug Dependence

Pavlovian Processes in Drug Tolerance and Addictions. In collaboration with the Social and Biological Studies Division, sociobehavioral researchers undertake both animal and human experiments on the role of conditioning factors in the development of drug tolerance and in the maintenance of and relapse to drug use. The animal research is a continuation of our years of work on the important role that conditioning factors may play in drug use. Previous work has been supported by a grant from the Natural Sciences and Engineering Research Council (NSERC), and we have just received another three-year grant from the Research Council.

The basic premise of the research is that the processes underlying drug tolerance involve an adaptive compensatory response that opposes the pharmacological effects of the drug. The development of conditional compensatory responses underlies the phenomenon of tolerance, and what is very important, these responses are under the control of cues that have reliably accompanied prior drug experiences. If an organism is exposed to these conditional cues in the absence of the target drug, the compensatory responses are activated and they resemble withdrawal symptoms. It has been theorized that such "conditional withdrawal symptoms" may provide an important *motivational* factor in drug relapse. The basic notion is that when a person is exposed to such cues (e.g., drug use situation, presence of drugs, others using), the body, as a result of classical conditioning processes (i.e., learning by association), prepares in certain ways to receive the drug. It is also assumed that the way in which the body prepares for the drug is opposite in effect to the actual actions of the drug on the body because this process, like other homeostatic biological processes, can be viewed as having the goal of maintaining equilibrium in the body. If the drug is a depressant drug, the body compensates for its expected consumption by reacting in the opposite direction (i.e., the person feels stimulated). It is postulated that this stimulated, or excitatory, reaction is aversive in nature unless it is followed by drug consumption, which counteracts the stimulatory effects. Thus, drug cues elicit an aversive state that can be alleviated by drug use (relapse). One aspect of our current work is to experimentally assess this theory of drug relapse.

Another aspect of our current work has focused on understanding the processes mediating the extinction of conditional compensatory responses, that is, the loss of tolerance. An understanding of these extinction processes clearly has important clinical implications. In previous work we have shown that a small dose of alcohol can serve as a potent conditional cue that governs tolerance to a large dose of alcohol. We have argued that this phenomenon can be viewed as a Pavlovian analogue of binge drinking. In the study, repeated presentations of the small dose alone mediated the loss of tolerance wherever "abstinent" animals retained their conditional reactions to the small dose. This finding would not be predicted except in the context of conditioning theory.

Implications of the Pavlovian theory of addiction have also been considered theoretically and investigated with humans. In one study, subjects who had a history of heavy drinking were exposed to alcohol-related cues or non-alcohol cues. The study demonstrated theoretically predicted changes in several indices after a single exposure to the alcohol cues but not to the non-alcohol ones. These changes are consistent with the elicitation of conditional compensatory responses by the alcohol cues. A second study confirmed the hypothesis that these

responses will extinguish with repeated exposure to the cues alone. These data represent an important illustration of the continuity in research that can range from theoretically based animal research to clinical trials in humans.

Alcohol Regulation in Humans. A new line of research has been initiated to assess the regulation of alcohol consumption in "heavy" and "light" drinkers. Subjects were requested to consume 18 mini-drinks while indices of mood, sociability and somatic status were monitored, and subjects rated the desirability of each mini-drink. Initial analyses indicate that the data were orderly, and divergent for the heavy and light drinkers.

For the heavy drinkers, their desire for each drink was an increasing positive function of the amount previously consumed. For the light drinkers, desirability ratings initially increased and then markedly decreased over the second half of each session. In addition, heavy drinkers showed more tolerance than light drinkers in all indices, except "affect" and "sociability," on which they showed greater effects of the alcohol. We believe that both the findings of the study and the general methodology are potentially important. At this stage, there are two general interpretations of the findings. One is that tolerance develops much more quickly to the aversive effects of alcohol than to the positive effects. This notion has long been suggested in the literature, but data on the issue have been saliently lacking. An alternative view is that there are large individual differences in the regulation of alcohol "highs." In this view, some subjects are biologically "set" to consume relatively large amounts of alcohol, whereas others have a much lower "set point" for alcohol "satiety."

Reinforcing Effects of Drugs — Benzodiazepines. A clinical study of benzodiazepine users (described in the previous *Research Digest*) indicated that regular use of low doses of benzodiazepines can be reinforcing. The goal of this project was to determine how the acute administration of benzodiazepines affected the appraisal of memories for past experiences. This is an important question because of our clinical impression that chronic use is often maintained in individuals whose appraisal of their experience gives rise to negative affect, the blunting of which can be achieved by benzodiazepines. The results indicated that diazepam positively enhanced ratings of memories (e.g., pleasanter, happier) compared to placebo. This effect was pronounced in female subjects but weak or non-existent in males. Interestingly, subjects of both sexes tended to dislike the effects of diazepam, an indication that the enhancement of the appraisal of memories is independent of the subjective appraisal of the drug effect as such. An implication of these findings is that a non-pharmacological cognitive reappraisal technique could be applied to achieve the same therapeutic result as benzodiazepines.

At present, this study is being replicated and extended by including the administration of amphetamine and chlorpromazine into the design.

Influence of Television Portrayals on Alcohol Use. The effects on viewers of television portrayals of alcohol use and of alcoholic beverage advertisements have been of concern for years. The few existing studies have not used alcohol-dependent subjects, although research suggests that they may be particularly prone to adverse effects from alcohol cues. In an initial study (see previous *Research Digest*) it was found that neither commercial type nor program type had any effect on subsequent drinking by normal drinkers.

A second study involves alcohol abusers who are not committed to abstinence. The dependent measure is change in subjects' scores on a measure of self-confidence that they could resist the urge to drink. A preliminary analysis revealed that subjects had significantly reduced self-confidence scores after viewing the program containing alcohol cues, but that the type of commercials viewed had no effect. This finding suggests that alcohol abusers may be placed at risk of relapse by alcohol cues that occur as part of television programs.

The Concept of Craving. The concept of craving for drugs is central to various hypotheses concerning the nature of drug dependence. The resilience of the term indicates the phenomenological appeal of the concept, but unfortunately attempts to operationalize it have been inconsistent, as has been the theoretical use to which scientists have put the term. Work in the department has led to a number of publications dealing with the concept; these have attempted to clarify the different theoretical constructs to which the term has been applied, to integrate the reported phenomena of craving on the basis of a single process (Pavlovian conditioning), and to incorporate such notions into models of relapse.

Boundary Model of Drug Taking. A second theoretical area is the "boundary" model of drug use. In essence, the model proposes that biological factors establish lower and upper boundaries to drug self-administration, and that these limits tend to be sufficiently well separated, particularly in experienced users, to permit considerable variation in drug use on the basis of sociobehavioral variables. Continued support of this work derives from an NSERC grant.

Dual-Process Theory of Memory. Our work on Korsakoff amnesia resulting from chronic alcoholism has resulted in the development of a novel dual-process theory of normal memory function. Thus, the applied research of the department has fortuitously yielded not only refinements of assessment procedures for the assessment of consequences of drug and alcohol use (see below: Neuropsychological Consequences of Alcohol Use) but also potentially important insights into the normal operation of a vital psychological process.

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2. Assessment of Drug-Dependent Persons

Valid clinical research on alcohol- and drug-dependent persons depends crucially upon the establishment of procedures for the objective measurement of the behavior of drug use, the characteristics of persons being treated to decrease their drug use, and the consequences of drug use. Thus, treatment research on substance abuse is inextricably linked to assessment research.

Given that direct observation of the behavior is generally infeasible, a major thrust of assessment research is in the construction of indirect measures of alcohol and drug use. Such measures require validation and assessments of reliability, and because measures of drug use constitute the principal outcome variables in all treatment research, this kind of assessment research has been, and continues to be, an important aspect of the activities of the department.

Measuring Levels of Alcohol and Drug Use.

a) Lifetime Drinking History. The Lifetime Drinking History is a structured interview that traces major phases in an individual's drinking career from the onset of regular drinking. A prototype version of the Lifetime Drinking History has been programmed for administration via a microcomputer. Work is under way on the development of a computerized assessment battery for alcohol/drug problems that would include the Lifetime Drinking History.

b) Timeline Assessments of Recent Drinking. The most commonly used methods for obtaining self-reports of ethanol consumption have been estimation formulae, wherein persons are asked to specify how they "typically" drank. An alternative procedure for assessing recent drinking history is the timeline (TL) method, wherein individuals are asked to recall their daily consumption over a specified time period.

As an extension of this line of research, the test-retest reliability of the TL method was recently assessed with adult normal drinkers from the general population, the only major subpopulation of adults for which reliability data are not yet available.

c) Self-Monitoring Methods. Self-observation and recording of drug-use behaviors by clients before, during, and after the completion of treatment has been used as a technique aimed at enhancing the accuracy of estimates of drug use. This procedure can have direct therapeutic benefit, and is also apparently superior to retrospective recall in assessing drug use. Procedures developed in the department have been used in many treatment research projects that we have conducted with multiple drug users, benzodiazepine users, problem drinkers, and heavy social drinkers participating in studies of pharmacological regulation of alcohol intake. In all these studies, the method has been found to be valid, and in treatment studies, data collected in this manner during treatment have been found to be predictive of outcome one year later.

An important issue concerning self-monitoring is whether it is reactive on the behavior monitored. A recent project investigated whether self-monitoring of alcohol consumption by college students is a reactive procedure. There was no evidence that self-monitoring was reactive with these subjects; however, it remains possible that for heavier drinkers and alcohol abusers self-monitoring could be reactive.

Innovative approaches to self-monitoring are the "stain-monitoring" and "color-matching" techniques that allow cigarette smokers to assess their exposure to cigarette smoke (see previous *Research Digest*). Research continues on the development of the color-matching technique. This technique depends upon the fact that intensity of tar stains on spent cigarette filters can be used to estimate how much smoke has been drawn through the filters. The color-scale has been refined, and some of the intrinsic limits of the color-matching system have been assessed. Further research is planned to evaluate the value of the color-matching scale in a program for secondary prevention of smoking.

d) Risks of Pipe and Cigar Smoking. Since the first Report on Smoking and Health of the U.S. Surgeon-General, pipe and cigar smoking has been advocated as a less hazardous alternative to cigarette smoking. Researchers concerned with the risks of pipe and cigar smoking have been preoccupied with the distinction between primary (never cigarette) smokers and secondary (former cigarette) smokers, on the grounds that secondary smokers tend to maintain the habit of inhalation when switching from cigarettes and therefore are smoking more dangerously than primary smokers who tend not to inhale. Our project has shown that direct questions about inhalation habits and daily frequency of pipe and cigar intake are much more useful as indicators of smoke exposure than the traditional primary/secondary pipe/cigar smoking distinction. We have also found that inhaling and non-inhaling smokers differ in the expressed reasons or motives for smoking.

e) Psychoactive Drug Use History. Multiple drug use is an increasingly common clinical problem, but there exist few standardized methods of assessing this behavior in a manner that permits repeated assessments at preplanned intervals. The Psychoactive Drug Use History was designed to meet this need for the Young Drug Abusers Study (see the section below on treatment research). This structured interview yields information on the frequency of use over the past year for ten classes of drugs (alcohol, cannabis, hallucinogens, narcotic analgesics, sedative/hypnotics, solvents, stimulants, tranquillizers, volatile nitrates, and miscellaneous others). Past and present problems with these classes are also assessed, and the time since the onset of problems is estimated. Initial evaluations of the procedure indicate that it yields valid information. Analysis of the data on frequency of use revealed four relatively independent dimensions of use. These are (1) "depressants" — narcotics, sedative/hypnotics, and tranquillizers; (2) "recreational drugs" — cannabis, hallucinogens, and stimulants; (3) alcohol; and (4) solvents. A cluster analysis revealed five clusters of users. Four of the clusters were represented by persons who were multiple drug users with one of the above dimensions of drug use being particularly salient. The fifth cluster (containing 23% of the sample) consisted of persons who were very heavy users of all drug classes except solvents.

A similar study of all Clinical Institute clients revealed that the alcohol-use dimension is probably an element of a drug-use factor, or dimension, involving use of alcohol, tobacco, and caffeine. This finding was replicated in a U.S. sample, and among the multiple drug users heavy tobacco and caffeine use was found to be associated with heavy alcohol use.

At present, the origins of these separate dimensions of drug use can only be speculated upon. However, the results of these studies indicate that a tolerably simple yet valid procedure has been described for assessing multiple drug use in evaluating treatment procedures.

Identification of Alcohol Abuse. The goal of this research line is to establish a short list, which can be readily implemented, of clinical and laboratory criteria for the identification of alcohol abuse.

Medical literature continues to draw attention to selected findings on clinical examination that may be related to excessive drinking. However, the possibility that clinical or laboratory indicators may be insensitive or redundant for the detection of alcohol abuse has not been explored in sufficient detail. A comprehensive set of clinical and laboratory information was acquired from three groups of subjects: outpatients with alcohol problems, social drinkers, and family practice patients. Findings from clinical examination provided greater diagnostic accuracy than laboratory tests for the detection of alcohol abuse. Logistic regression analyses produced an overall accuracy of 85–91% for the clinical signs, 84–88% for the medical history items, and 71-83% for the laboratory tests in differentiating the three groups. Further analyses revealed 17 clinical signs and 13 medical history items that formed a highly diagnostic instrument (Alcohol Clinical Index) that could be used in clinical practice. A probability of alcohol abuse exceeding 0.90 was found where four or more clinical signs or four or more medical history items were present on the Alcohol Clinical Index.

A study with similar rationale, conducted in a Norwegian alcohol clinic, also indicated the value of clinical signs in detecting alcohol abuse. Pilot work showed that insomnia, hypertension, and gastric symptoms were frequently observed among patients. Such symptoms tend to appear at an early stage of problem drinking. The relative sensitivities in differentiating new patient admissions from repeat admissions were evaluated for three symptoms and four biochemical markers of heavy drinking. Clinical symptoms of insomnia and gastric problems were frequently present in both groups. In contrast, elevations of gammaglutamyl transpeptidase (GGT), mean corpuscular volume (MCV), SGOT, and SGPT were common only in the repeat admission group.

An innovative extension of strategies for early identification of alcohol abuse involves the use of screening by microcomputer in primary health care settings in the community. At present, the approach is being integrated with early intervention techniques designed for primary-care health professionals. This line of research is receiving grant support from Health and Welfare and the Ralston Medical Research Foundation. The overall goal of this aspect of the research is to devise procedures for early detection of problem drinkers in a variety of health and social service settings. A general lifestyle assessment administered via microcomputer is being examined for this purpose. It looks at a variety of factors including nutrition, physical exercise, sleep, weight, physical abuse, sexual activities, stress/anxiety, and life satisfaction. Thus, the alcohol section is embedded within a much broader lifestyle assessment. A major evaluation of the Computerized Lifestyle Assessment is being conducted with patients visiting their family doctor at the Family Practice Service of Toronto General Hospital.

Assessment of Consequences of Alcohol and Drug Abuse. The severity of problems associated with excessive use of drugs tends to be a predictor of treatment outcome and a sound basis for selecting the nature of the treatment that a client should receive. Hence, instruments that assess such problems in a standarized manner are extremely useful in planning treatment, and in describing important characteristics of clinical and research samples.

a) The Alcohol Dependence Scale (ADS). ADS was developed to provide a quantitative measure of the alcohol dependence syndrome, which is a central concept in the World Health Organization (WHO) classification of alcohol-related disabilities. A major evaluation study found that the syndrome can be assessed quite reliably by ADS, and that ADS was correlated in predictable ways with clinic attendance, physical symptoms, and psychosocial problems. Guidelines for the administration, scoring, and interpretation of this instrument have been prepared, and it has generated considerable interest internationally.

b) The Drug Abuse Screening Test (DAST). DAST has been incorporated along with the Alcohol Dependence Scale in the Structured Addictions Assessment Interview for Selecting Treatment (ASIST) developed by the Foundation for use in assessment/referral centres across the province. Both DAST and ADS are included as part of the Computerized Lifestyle Assessment that is being evaluated in various health care settings. A recent study has used DAST to provide evidence for a drug-dependence syndrome among narcotic users.

c) Neuropsychological Consequences of Alcohol Abuse. Neuropsychological research within the Sociobehavioral Research program is a part of the larger research effort within the Clinical Institute to study the relationship between alcohol and drug abuse and brain function. Treatment projects often include tests of neuropsychological functioning in patients in order to answer specific questions (e.g., consequences of long-term benzodiazepine use). These "spin-offs" from treatment projects have been made possible because of the methodologies developed in study of the organic brain syndrome and its reversibility. The current emphases of this research are to continue the controlled study of the reversible aspects of the alcohol organic brain syndrome, and to assess the nature of the memory deficit in amnesic (Korsakoff's) alcoholics.

One of the principal recent advances in this area of research has been the development of a two-process theory of normal memory function. This theoretical work developed out of the study of the alcohol amnesic syndrome. Recently, the theoretical account has been extended to describe the memory impairment of non-amnesic alcoholics. The research of the department continues to indicate that two etiologically distinct organic brain syndromes are related to chronic alcohol consumption. The first involves deficits of abstraction and problem solving, and appears to be related to alcohol consumption. The second involves memory and cerebellar functions, and is probably caused by thiamine deficiency. Consistent with the hypothesis of two syndromes of alcohol-related impairment, our research has recently shown that measures of the sensitivity of tests in differentiating alcohol abusers from social drinkers are predictably correlated with the strength of association between test score and CT-scan indices of cerebral atrophy only in non-amnesic subjects. This finding convergently validates the neuropsychological and CT assessments procedures. This research line has been supported by a grant from NIAAA.

d) Benzodiazepine-Induced Memory Impairment. We have been assessing the effects of benzodiazepines on a wide variety of information-processing and memory tasks. This research clearly shows that benzodiazepines *selectively* affect some memory processes whereas others appear totally unaffected. Such research may further our understanding of the pattern of cognitive deficits that develop with prolonged drug abuse.

Typologies of Alcohol and Drug Abuse. A currently influential hypothesis is that different types of drug-dependent persons benefit from different types of treatment. Hence, clients should be matched to appropriate treatments. If the hypothesis is to be tested, different types of clients must be validly described. One method of differentiation is on the basis of substance used, or pattern of substances used (see above section on Psychoactive Drug Use History). Within drug classes, differentiations may also be made. In a recent study using an extensive cluster-analytic design, three distinct types of drinkers were identified and the typology replicated among a large sample of individuals seeking help for alcohol-related problems. Type A (early-stage problem drinkers) represented a fairly heterogeneous group who showed evidence of drinking problems but had not accrued major symptoms of alcohol dependence. Type B (affiliative, moderate alcohol dependence) drinkers were more socially oriented and tended to drink on a daily basis. Type C (isolated, severe alcohol dependence) drinkers were more socially isolated, tended to drink in binges, and reported the most severe symptoms of alcoholism. There were consistent differences in symptom severity among the three types on measures of psychopathology, cognitive functioning, and social adjustment. A hybrid model was proposed that consisted of the three types superimposed on an underlying continuum of alcohol dependence.

In a methodological study, data obtained from problem drinkers by the timeline method in outpatient treatment were analysed with a cluster-analysis technique developed by Foundation scientists. Daily drinking data were obtained for the year prior to the start of treatment and through the 18 months following. Five profile types were identified. The most interesting feature of the profiles was that many clients fit a pattern showing marked improvement in their drinking behavior during the month prior to entering treatment, with the improvement then maintained over the course of treatment and follow-up.

Assessing Variables Related to Drug and Alcohol Use.

a) Situational Diagnosis of Drinking Risk. It has become increasingly recognized that clients vary in terms of the types of situations or events that are associated with excessive drinking, and that identification of these high-risk drinking situations can be of importance in planning treatment. The Inventory of Drinking Situations is a 100-item self-report questionnaire (IDS-100) that was developed to provide the therapist with a situational diagnostic profile of drinking risk for an alcoholic client seeking treatment. Factor analysis has supported the use of an eight-category profile of drinking situations. Further psychometric work has resulted in the development of a short form of the questionnaire (IDS-42). Norms are now available for males on both the IDS-100 and the IDS-42. It has been found that client responses on the IDS agree well with the frequency of relapses occurring in drinking risk categories reported in the literature; over two-thirds of the clients had their highest risk situation for drinking on the IDS in response to negative emotional states (39%), interpersonal conflict (17%), or social pressure to drink (12%).

Client self-efficacy in coping with a range of high-risk drinking situations has been found to be an excellent predictor of outcome. The Situational Confidence Questionnaire (SCQ-100) was developed as an aid to therapists in monitoring a client's progress in treatment. As with the IDS, an eight-category classification system is used to categorize high-risk drinking areas. Psychometric work has resulted in two short forms of this questionnaire (SCQ-42 and ACQ-16). Responses on the questionnaire have been found to be predictive not only of the likelihood of relapse but also of the type of situation in which relapse is most likely to occur.

b) Recall of Life Events. The test-retest reliability of a life events questionnaire assessing alcohol abusers' self-reports of distant life events was found to be reliable. (See previous *Research Digest*.) New analyses indicate that concordance, which measures exact item agreement, was similarly high. A unique aspect of this study involved probing subjects' reasons for their having given inconsistent answers in the two interviews. Inconsistencies often resulted from errors in the temporal placement of events or from misunderstanding items on the questionnaire, rather than from a failure to recall events. A recent project demonstrated that using memory aids prior to completing a life events questionnaire increased the test-retest reliability of reported events. These studies represent an evolving line of research intended to develop procedures specifically for reducing different types of reporting errors in recalling life events.

c) Family Interactions. A variety of theoretical and empirical work indicates that the nature of family relationships can be importantly related to excessive alcohol and drug use. Hence, some activity of the department is aimed at developing standardized procedures for assessing such relationships.

Considerable efforts have been directed at the further development and validation of the Family Assessment Measure (FAM). This instrument is based on a process model of family functioning that integrates different approaches to family therapy and research. FAM is a self-report instrument that provides quantitative indices of family strengths and weaknesses in seven areas: task accomplishment, role performance, communication, affective expression, involvement, control, and values and norms. FAM consists of three components: (1) a General Scale, which focuses on the family as a system, (2) a Dyadic Relationships Scale, which examines relationships between specific pairs in the family, and (3) a Self-Rating Scale, which taps the individual's perception of his/her functioning in the family. Thus, each scale provides a different perspective on family functioning. Empirically, analyses have shown that the FAM scales are quite reliable, and that they significantly differentiate between problem and non-problem families.

A major validation project is currently under way, in collaboration with the University of Pittsburgh, involving three types of families: (1) the father is alcoholic, (2) the father is depressed, (3) the father is normal. Preliminary analyses have shown that the FAM significantly differentiates among the three types of families. Specifically, the alcoholic-father families tend to

report a broad range of problems related to task accomplishment, communication, involvement, and roles. This research is supported in part by a grant from NIAAA.

A further study was undertaken to examine the interdependence of alcohol abuse and marital adjustment. Emphasis was placed on investigating how different patterns of alcohol use vary with different levels of marital satisfaction and how such relationships might be mediated by the sociobehavioral consequences of problem drinking within the family. The study sample comprised couples who completed the one-year follow-up in the Marital Systems Study. It was found that the likelihood of marital disruption was greater in heavy-drinking households than in non-heavy-drinking households. However, differences between heavy-drinking and non-heavy-drinking settings became largely non-significant when the number of sociobehavioral consequences of alcohol use for the marriage was statistically controlled. These data suggest that the extent to which problem drinking interferes with the everyday functioning of the family may determine the level of distress in the marriage.

d) Assessing Family History of Alcohol Problems. No research has previously addressed the test-retest reliability of the self-reported family history of alcohol problems. A study was therefore conducted using a family-tree method of obtaining information. High test-retest reliability was found for reports of the family history of drinking problems, especially as regards first-degree relatives. The family-tree questionnaire has applicability for both treatment and basic research.

e) Social Anxiety in Alcohol Users. Because social anxiety is considered to be an important determinant in the drinking behavior of many alcoholics, elucidation of the mechanisms mediating the relationship between interpersonal dysfunction and alcohol abuse should have implications for the understanding, assessment, and treatment of alcohol problems. As a first step in developing this model, problem drinkers are being evaluated along four dimensions: autonomic arousal, skill deficit, cognitive impairment, and metacognitive self-awareness. In this project, two sets of measures assessing different aspects of social anxiety are administered. The first set consists of self-report instruments that measure a predisposition for each of four clinical components, or "traits," in social anxiety. Present levels of severity along each of these dimensions will be evaluated with a second set of "state" measures obtained in the context of a situational behavioral assessment. Self-report, behavioral, and physiological measures of arousal/distress, cognitive-evaluative impairment, skill level, and self-consciousness will be obtained while subjects participate in a stressful social interaction. Factor analysis will be used to confirm social anxiety subtypes, their convergent and discriminant validity, and their relation to various indices of alcohol/drug use.

Comprehensive Reviews of Assessment Procedures. In addition to developing and evaluating novel assessment procedures, investigators in the department also produce scholarly reviews of various aspects of assessment, usually at the invitation of agencies controlling funding for treatment services (e.g., NIAAA) or editors of authoritative publications (e.g., *Research Advances in Alcohol and Drug Problems*). Among the topics reviewed in the period of this report are: intake assessment procedures for alcohol- and drug-dependent persons; methods for evaluating treatment outcome; neuropsychological and neuroradiological assessment of alcohol abusers; assessment of recent alcohol and drug consumption; and assessment of exposure to tobacco smoke, using biochemical and behavioral methods.

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3. Sociobehavioral Treatment Research

Stated simply, the objective of behavioral treatment for substance abuse is to provide techniques that are effective, economical, and transferable to the larger treatment community beyond the Foundation. In practice, however, there are many issues embedded in this enterprise. Therefore, treatment research may be directed toward the evaluation of a specific type of intervention, a special population, a particular substance, or a meta-treatment question (such as the efficacy of extremely brief interventions). Typically, major treatment projects reflect more than one such substantive concern, and methodological issues are often addressed as well.

The Controlled Drinking Study. The study involved random assignment of 70 socially stable problem drinkers to a cognitive-behavioral outpatient program, with the goals of either abstinence or moderation of drinking (see previous *Research Digest*). The clients assigned to the goal of controlled drinking were more accepting of the assigned goal, drank significantly less during treatment, and requested significantly fewer aftercare sessions than those assigned to abstinence. At all of the follow-ups, from 6 months to 24 months, the two groups did not differ in outcome. Both groups showed significant reductions of consumption, and the large majority were consuming moderate quantities of alcohol regardless of the assigned goal. Overall, more than 70% of the clients were found to have a satisfactory outcome over the two years of follow-up.

On the basis of the results, the authors concluded that provision of treatment that permits the option of a goal of moderation is most suitable for problem drinkers of the type recruited into the study. A manual for therapists, based upon the techniques developed in this program of research, has been published by the Foundation.

Three additional findings have emerged from further analysis of the data. About 40% of the clients reported having at least one parent with an alcohol or drug problem. These clients did not differ from the others on a variety of characteristics, though they did tend to show evidence of higher levels of alcohol dependence. At follow-up they differed from the others in that they reported significantly lower levels of consumption. Though they consumed the same quantities as other clients on days when they consumed alcohol, they had significantly more abstinent days. Though most were moderate drinkers, they were

more conservative than the others in their pattern of moderate consumption.

A second matter related to the levels of alcohol consumption reported to be associated with problems or problem-free. This issue is of importance for therapists wishing to counsel clients about levels of drinking when moderation is the goal. The cutoff for "moderate drinking" in the outcome study was set at 20 standard drinks per week, a cutoff that has been used in previous studies. However, some clients who reported drinking at this level had some adverse consequences. The level of consumption found to best differentiate consumers having problems from those who claimed to be problem-free was no more than four drinks per day three times a week. This is suggested as a rule of thumb for therapists asked for advice about "How much is too much?"

Finally, a complex analysis of levels of consumption at pre-treatment, during treatment, and at follow-up indicated that assignment to goal was unrelated to outcome for clients who were in the lower half of the consumption range before treatment. Among the heavier-drinking group, however, the odds of successful abstinence and moderation during the phases of treatment were better for the clients assigned to the controlled drinking condition. This finding is interpreted by the authors as suggesting that for subjects drinking below the group average (about 50 standard drinks a week) no more than minimal treatment or advice may be necessary. On the other hand, for problem drinkers with social stability and intact cognitive function, and drinking in the range from 50 to 120 drinks a week, a brief outpatient treatment with flexible treatment goals appears to confer an advantage compared to assignment to abstinence. It is important to note that clients assigned to the controlled drinking condition could opt for abstinence (i.e., had choice), whereas those assigned to abstinence did not. Thus this finding, and others of the study, may relate to flexibility of goals and client choice as much as to training in moderate drinking.

The study has had various research ramifications in the Clinical Institute. As part of a large study on use of benzodiazepines, the procedures described in the therapist's manual were adapted for persons who were using prescribed benzodiazepines up to doses of 40 mg diazepam a day or equivalent and who sought help to discontinue use. The study involved placebo-controlled abrupt withdrawal or tapering of the medication. Results of client self-monitoring and blood analyses indicated a clear withdrawal syndrome to these levels of benzodiazepine use over prolonged periods, and a higher frequency of "drug supplementation" in the placebo group. However, at follow-up at 3, 6, and 12 months, there was no superiority of outcome in the tapered group.

For alcohol users the treatment package has been further developed. It has been further abbreviated for use by primary health care agents, and is at present being evaluated in the hands of physicians in a family practice unit of a general hospital and in a form in which the brief intervention is self-administered by the client interacting with a microcomputer. (This project is part of a large-scale evaluation of secondary prevention, which also involves the evaluation of the Computerized Lifestyle Assessment. The research is supported by Health and Welfare Canada.) In the Clinical Institute, the treatment is being compared when dispensed according to the therapist's manual, dispensed as therapist-guided use of its content in the form of a self-help manual, and as a brief intervention of two outpatient sessions.

Treatment of Multiple Drug Dependence. There are no controlled studies of treatment for multiple substance abuse. A large treatment outcome study was designed to compare three treatment programs for this population. The study embodied four main objectives: (1) to describe patterns of drug use in young persons presenting for treatment; (2) to compare the effectiveness of two broad-spectrum behavioral residential programs (3–6-week inpatient) with a brief (3-session) outpatient treatment focused on training in self-control procedures for the avoidance of drug use; (3) to contrast the two inpatient conditions in which treatment components were identical, but the ward milieu was established via use of a "credit" system in which prosocial behaviors and progress in treatment were reinforced on either a group-contingent or a client-contingent basis; (4) to develop a measure of the perceived self-efficacy of the clients with respect to avoidance of drug use and other areas of functioning. The project is completed, and initial findings relating to each of the objectives have been presented.

An initial examination of the relative effectiveness of the inpatient and outpatient treatments involved ratings of the outcomes of the subjects, using the drug use data from one-year follow-up, compared to assessment scores. Subjects were rated independently by four judges, and categorized as successful outcome, significantly improved, or unimproved. When all subjects not reached for follow-up (about 25%) were rated unimproved, the results indicated that the group-contingent broad-spectrum condition yielded superior outcome to both client-contingent and outpatient self-control training (SCT), which did not differ. The superiority of the group-contingent condition may be important, but it is a preliminary finding that awaits confirmation by more refined analysis. Such analysis is rendered possible by the simplification of the data on drug use previously described (Psychoactive Drug Use History). It is also worth noting that 60% of the clients treated with the brief counselling (SCT) were at least "significantly improved" after one year, a finding very similar to those receiving the more intensive client-contingent broad-spectrum treatment.

Certain types of drug abuse have the reputation of particular resistance to treatment. In the present sample there was no evidence that either solvent users or heavy users of cocaine were less successfully treated than other groups.

The reliability of self-reports of use of illicit drugs tend to be even more suspect than reports of alcohol consumption. Hence validation of such data was an important consideration in the Young Drug Abusers study. Two approaches have been taken. First, at follow-up, reported use of cannabis was validated by means of urinalysis. The results indicated that the self-reports were valid, and that recent cannabis use was more likely to be identified by self-report (under the conditions of this study) than by urine screening. Furthermore, the one-year history of drug use was validated convergently at follow-up by the demonstration that it was lawfully related to variables measuring social stability, employment, social network, and various other treatment-relevant variables.

Apart from work on the psychometric properties of an initial draft of the self-efficacy scale in the pilot phase of the study, this aspect of the study has not yet been evaluated. However, a study of the subjects in the brief SCT treatment condition yielded results that are probably related to this construct. At assessment clients were asked to identify the number (from a choice of 11) of goals they had in various life areas (e.g., drug use, family problems, assertiveness). The number of goals was used as a measure of problem multiplicity in the client. In addition, for each identified goal, the client was asked to indicate whether he/she required professional assistance to achieve the goal. The fewer the requests for professional assistance, the higher the client scored in a measure termed self-reliance. Problem multiplicity and low self-reliance were found to be good predictors of unsuccessful outcome at one-year follow-up, as well as drug use during treatment, success in achieving initial treatment goals, and dropout from treatment. Various measures assessed as indices of client motivation did not differentiate the outcome groups. Hence, measures collected during assessment and the early phases of treatment may be useful in making empirically based decisions about the intensity of treatment that clients should receive.

Relapse Prevention Training. The failure to maintain a change in drinking behavior over time following discharge from treatment is a major concern to professionals in the alcoholism treatment field. Relapse rates of clients have typically been running to over 60% within the first three months after treatment discharge. From a social-learning theory perspective, the treatment implications of a failure to maintain change are very different from the treatment implication of a failure to initiate change. Drawing upon what is known about the maintenance of behavior change, a relapse prevention treatment program for alcoholics has been developed and is undergoing research investigation in the Clinical Institute.

In an employed problem drinker program at the Foundation, 41 clients presenting for treatment participated in a clinical trial in which they received relapse prevention procedures. Detailed documentation was kept of each client's drinking-risk areas and associated self-efficacy ratings, the source, type, and outcome of all homework assignments undertaken over the course of treatment, and the situational determinants of any drinking that occurred. Clients performed a mean of 42 assignments each over the course of the three-month program, for an average of 3.5 assignments a week. As predicted, there was a marked improvement in reported self-efficacy in dealing with drinking-related situations. Client daily self-monitoring forms indicated that the percentage of abstinent days for all clients over the three month program was high (mean = 91%; SD — 20). Heavy drinking episodes were much more likely to occur in response to negative emotional states, and light drinking episodes in response to intra- and interpersonal positive emotional states. These findings suggest that situations involving negative emotional states may be more likely to result in serious relapse.

An important issue relates to whether self-efficacy ratings taken at intake to treatment allow the therapist to identify the client's weakest areas — that is, the areas in which the client is most likely to relapse. It was found that efficacy scores at intake successfully predicted the specific nature of the situation in which relapse to heavy drinking would occur. Self-efficacy ratings can provide the therapist not only with a useful tool for monitoring the progress of the client over treatment, but also a blueprint of the areas in which the client is still vulnerable and requires further work before discharge from treatment.

Two randomized-control clinical trials testing the efficacy of the relapse prevention program are under way. In the first trial, the relapse prevention procedures are being compared to more traditional methods of aftercare; follow-up data collection has now been completed and data analysis has begun. In the second trial, the value of the relapse prevention procedures in teaching alcoholics to use a short-acting alcohol-sensitizing drug (citrated calcium carbimide) in anticipation of high-risk drinking situations is being compared to the more traditional method of prescription of this drug by physicians; the clinical intervention phase of this study is still in progress.

Guided Self-Management Project. The Guided Self-Management Project is evaluating the relative effectiveness of two treatments (behavioral counselling and relapse prevention) specifically designed for persons who have alcohol problems but who are not severely dependent on alcohol. Each program has the same basic structure. Treatment involves a comprehensive assessment, short readings and homework assignments, two formal 90-minute treatment sessions, and two years of follow-up. During treatment and follow-up, clients are informed that they should feel free to request additional treatment. This allows for further treatment when needed, while not unduly imposing upon clients who do well with short-term treatment. On the basis of the pilot study and formal study to date, it can be stated that the treatment programs are well received by clients. There are preliminary indications that for many problem drinkers the situations when they are at high risk for heavy drinking are when they are experiencing positive feelings. By contrast, severely dependent persons frequently report their heavy drinking as tied to situations characterized as negative emotional states. These indications confirm findings from the controlled drinking study and the relapse prevention project.

Social Support Project. Another current project will examine prospectively whether treatment effectiveness can be improved by systematically incorporating social support into treatment. Participation is available to clients who have a spouse willing to be involved in the treatment. Clients participate in the Clinical Institute four-session behavioral outpatient treatment program augmented by the incorporation of procedures used in the Guided Self-Management Project. Clients are randomly assigned to two groups: Natural Social Support and Directed Social Support. All spouses attend two education/information sessions, which occur at about the same time as the clients' first and last treatment sessions. At these sessions, spouses of the Natural Social Support group are presented with information to provide them with (1) a better understanding of why their spouse sometimes drinks heavily, (2) an understanding of the nature of the treatment program, and (3) a realistic and long-term perspective on recovery. Spouses in the Directed Social Support group are given the same information as those in the Natural

Social Support group, but in addition they are encouraged to (1) act as a continuing agent of treatment, (2) take a personal role in their spouse's recovery, (3) support their spouse's resolving the drinking problem, and (4) understand that how they view recovery and respond to potential or actual slips is critical to their spouse's long-term recovery.

The Marital Systems Study. The project involves a systems-oriented approach to treatment of alcohol abuse in which couples are treated conjointly, the assumption being that the marital unit has an important bearing on the problem and on the outcome. The project is designed to assess the efficacy of eight sessions of conjoint therapy, but of equal importance is the inclusion of a comparison in which "minimal care" (a single session of clearly specified advice) is offered. The "minimal care" alternative comes from an influential study conducted in Great Britain.

The results of the study indicated that both conjoint therapy and advice counselling groups significantly improved in drinking behavior and in marital adjustment over the course of the period of treatment and follow-up. However, a single session of advice counselling proved to be as effective in terms of reducing drinking and enhancing marital satisfaction as a regimen of eight sessions of conjoint therapy. In addition, the clients in both treatment conditions indicated a high degree of satisfaction with the service they received. In further analyses the possibility of differential responsiveness to the two approaches by different types of clients will be explored, in an effort to identify strategies to maximize the gains of treatment.

Coping Skills and Relaxation Training. The purpose of this project is an evaluation of three stress management programs with respect to their effectiveness in reducing alcohol and drug use in persons identified as alcohol abusers. Specifically, the study is a multiple comparison of: (a) a stress management program (SM) comprising a generic set of cognitive strategies aimed at the identification of natural stressors, their cognitive-social-behavioral concomitants, and adaptive coping patterns; (b) the stress management program combined with training in progressive muscular relaxation (SM/PMR); (c) the stress management program combined with training in Benson's meditation-relaxation (SM/M); and (d) a comparison condition consisting of primary care as at present provided at the Clinical Institute. The PMR and meditation conditions both include the stress management program because the identification and analysis of stress is seen as a logical and clinical prerequisite for the application of relaxation countermeasures to stress. The primary-care comparison condition allows for an evaluation of whether the three intensive stress programs offer benefits beyond those derived from the minimal treatment offered to all clients of the Clinical Institute.

The cognitive stress management approach, although widely used clinically, is characterized both by variety in its applications and by a paucity of data from controlled studies regarding its effects. In contrast, the PMR and meditation approaches have been subjected to considerable empirical scrutiny, but the studies have been methodologically flawed and the resulting data equivocal. Specifically, the majority of the research has involved subjects other than substance abusers, a point that raises questions regarding the generalizability of the findings to this population.

To date half of the projected sample have received the treatment.

Treatment of Tobacco Dependence. As part of the department's increased emphasis on tobacco research, we have initiated clinical and research programs on the treatment of tobacco dependence.

a) Smoking and Alcohol and Drug Problems. Our research has confirmed that over 80% of Clinical Institute clients with alcohol problems are also regular cigarette smokers. Although smoking has declined in the past ten years in the general population, there has been little change in smoking by alcoholics. We are conducting a study on the acceptability of Nicorette (a brand of nicotine-containing chewing gum) as a smoking cessation aid for clients in the program for employed clients. Such a multi-drug-using group is considered an especially difficult group in which to achieve modification of smoking habits. This project should lead (a) to a better characterization of the smoking habits of persons with other substance problems (by means of biochemical measures of smoke exposure) and (b) to the development of treatment programs that will increase smoking cessation. (External funding to support this project has been obtained from Merrill Dow Canada and A.B. Leo, Sweden.)

b) Monitoring the Ontario Lung Association Countdown Smoking Cessation Program. The Ontario Lung Association offers a state-of-the-art, low-cost, group smoking-cessation program throughout the province. We have entered into a collaboration with the Lung Association to monitor the success (and processes) of the program by means of a computer database at the Foundation. In addition, we are using this database to develop improved measures of tobacco dependence. The Lung Association has provided a small grant to help defray the costs of this project.

Investigators: H.M. Annis, H.D. Cappell, L. Hartman, S. Herling, F. Klajner, L.T. Kozlowski, G. Leigh, J. Peachey, M. Sanchez-Craig, H.A. Skinner, L.C. Sobell, M.B. Sobell, D.A. Wilkinson, A. Zweben

4. Systems-Oriented Research

Some of the research conducted in the department has its impact on systems in society related to the development, maintenance, or cessation of excessive drug use. Much of this research relates directly to health care systems, but some is relevant to drug distribution systems and to scientific systems.

A research issue of particular concern in the department is the cost-effectiveness of treatment. A steadily accumulating body of evidence indicates that although the majority of persons with alcohol and drug problems do not receive treatment, among those who are treated resources are frequently inefficiently used. The most comon cause of this inefficiency is that persons receive costly and intensive treatments where much briefer and more focused interventions would be at least as effective. A related issue is that natural remission of alcohol and drug problems is not uncommon, but the processes by which this important

phenomenon occurs are little studied and therefore poorly understood. A variety of research in the department addresses these issues either directly or indirectly.

Natural Resolution of Alcohol Problems. Research on the natural history of alcohol problems involves studying them from the perspective that nothing has altered their natural course; that is, the problems have not been professionally treated. There are two important reasons for such a study. First, since persons in treatment programs are but a small proportion of those who have alcohol problems, our understanding of this disorder may be biased if we base it only on those treated. Second, an understanding of what contributes to natural recoveries may indicate factors that can be incorporated and tested in treatment.

It has been suggested that natural recovery from alcohol problems is more common than previously suspected. Unfortunately, however, the small number of existing studies have serious methodological weaknesses. The Natural Resolution of Alcohol Problems study attempts to rectify some of the problems previously noted in this area of research. The study involves interviewing persons who have achieved a stable (at least three-year) recovery from alcohol problems without benefit of formal help or treatment, with the objectives of identifying factors related to recovery and to the maintenance of recovery. The study improves upon existing studies in several ways, including the important feature of a "non-resolved" control group. These non-resolved control subjects are interviewed about life events they experienced during a randomly selected year several years earlier (to control for memory differences between the resolved and non-resolved groups).

All subjects for the project are recruited through the media. Some volunteers reported that they had received treatment at some time prior to their resolution (often several years earlier) but felt they had fully resolved their problem on their own. We felt that this group might provide interesting data, and thus the study was expanded to involve four groups of subjects: (1) Resolved Abstinent (RA), who have resolved their drinking problem on their own through abstinence; (2) Resolved Non-abstinent (RNA), who have resolved their drinking problem on their own and whose drinking after resolution meets explicit criteria as non-hazardous and without evidence of alcohol-related problems; (3) Resolved, Abstinent Treatment (RAT), who responded to media solicitations for subjects and reported that although they had received formal help or treatment, usually in the distant past, they had found the treatment not to be helpful and later resolved their drinking problem on their own; (4) Non-resolved (NR), who have had a drinking problem for a minimum of five years, had a drinking problem when interviewed, and who have never received formal help or treatment for their problem.

Subjects and collaterals in the first three groups, and more than 30 subjects in the NR group, and their collaterals, have been interviewed. Although data analysis is just beginning, the interviews have resulted in the collection of a wealth of information on the natural history of alcohol problems. Various characteristics of the groups have now emerged. The number of subjects in each group are RA = 67; RNA = 21; RAT = 29; NR (incomplete sample) = 33. The MAST scores suggest that the abstinent subjects tended to have experienced more consequences of drinking than the non-abstinent before resolving their problem, though the durations of the problem and of its resolution are very similar. Initial indications suggest that about one-half of those subjects who had resolved their drinking problem and who had also smoked cigarettes at one time have also stopped smoking. Temporal relationships between stopping smoking and stopping drinking will be explored further as part of the data analyses. In addition, although the solicitation of subjects for the Non-resolved group specifically stated that the study was not a treatment study, during the interview many respondents asked about what types of treatment were available for their problem. Of the 33 subjects in the Non-resolved group to date, eight have subsequently entered a treatment program and six have been given a self-help manual at their request.

Research on Treatment Systems

a) Cost-Effectiveness. In view of the need to increase the cost-effectiveness of health care service-delivery systems, a review was made of the scientific evidence on the cost-effectiveness of traditional inpatient hospitalization for alcoholics compared with available alternatives. Results indicated that (1) most alcoholics in withdrawal can be safely detoxified in non-hospital-based units or on an ambulatory basis; (2) in-hospital alcoholism programs of up to a few months' duration have no higher success rates than hospital stays of a few days; (3) day treatment and outpatient programs have as good results as inpatient programs at a fraction of the cost; and (4) alcoholism treatment outcome results are likely to be improved by matching clients' needs to a range of treatment options. The Ministry of Health has made extensive use of this research report. An invited editorial by a member of the department on the issue of use of treatment resources appears in the *British Journal of Addiction*, October 1986.

Chronic alcoholics of low social stability often use services repeatedly without success. Many drop out of treatment, and the majority return to heavy drinking within the first three months of their discharge. Using volunteers as support agents might serve to reduce dropout rates and enhance treatment outcomes. A controlled study was designed to test this hypothesis. Clients were paired with a volunteer who had been trained to provide appropriate support. Volunteers attended treatment sessions with the clients and met with them in the community to help them put into practice tasks generated during treatment. The control group received the same amount of treatment, but clients were not paired with a volunteer. The feasibility of volunteers' providing supportive counselling at home was also assessed in a second study. On the basis of this work a Training Manual for Volunteers has been developed (in press) in which directives are provided for the recruitment, training, and deployment of volunteers in addiction treatment services. The manual contains a description of the participation of volunteers in the program, and the results of their intervention during treatment.

b) Reactive Effects of Follow-up and Self-Monitoring. Behavioral treatment programs for alcohol-dependent persons have often employed frequent follow-up contacts by a research worker and client self-monitoring of alcohol use in evaluating treatment outcome. It has been suggested that these intensive follow-up procedures may themselves serve a continuing care function. An

experimental study was designed to determine whether frequent follow-up contacts by a research worker had a demonstrable reactive effect on treatment outcome results, and whether self-monitoring procedures had effects over and above the effects of frequent follow-up contacts. No such effects were found. It would appear that such follow-up procedures can be used without creating appreciable reactive effects on the assessment of treatment program outcome.

c) Cross-Study Research. A number of other issues of concern in interpreting outcome results in the alcohol-dependence treatment field are being investigated. This line of research is made possible through the existence of standardized intake, within-treatment, and follow-up data-gathering procedures across clients involved in treatment outcome studies in the Clinical Institute. Planned studies will assess the following: (1) the role of pretreatment, treatment, and posttreatment variables in alcoholism treatment outcome; (2) the temporal stability of treatment outcome results; (3) the prediction and long-term prognoses of non-problem drinking versus abstinence; and (4) secondary drug use in alcohol abusers pre- and posttreatment. Data for this work have now been entered in the computer and are ready for analysis.

Research on Systems of Distribution: The Influence of Pack Size on Self-Reports of Smoking Rate. In a cross-cultural comparison of the sales of cigarette packages of 25 and 20 cigarettes each, we have identified that the availability of packs of 25s has a dramatic effect on the self-reporting of smoking rates of 25 per day. The majority of cigarettes in Canada are sold in packs of 25; 25s are just being introduced in the U.S. As the sales of 25s increase, a systematic alteration in self-reported intake is expected. (The recent introduction of packs of 30 cigarettes in Canada raises similar questions about changes in self-reports of smoking in Canada.) Studies are being planned to evaluate the effect of pack size on actual smoking rates and smoke exposure. If pack size influences smoking, it may be important to take steps (e.g., selective taxation) to discourage package sizes that lead to higher daily exposures to cigarette smoke.

Methodological Research. Scientists in the department made some contributions that are aimed at improving the conduct of sociobehavioral science. Examples of this type of research would include the development of novel statistical methods, such as Modal Profile Analysis, that are of value in describing populations in which we are interested, but clearly have much wider application.

In a quite different vein, investigators have contributed to the development of improved terminology and diagnostic criteria in the study of drug dependence. This type of contribution aims specifically at improving the quality of research within the scientific system conducting research on addictions.

Investigators: H.M. Annis, G. Leigh, L.T. Kozlowski, A. Osborne, M. Sanchez-Craig, H.A. Skinner, L.C. Sobell, M.B. Sobell, D.A. Wilkinson

COMMUNITY SERVICES DIVISION

The Community Services Division initiates a wide range of programs across the province that are designed to prevent alcohol and drug problems and to develop and improve services necessary for their treatment. Accordingly, the division's research focus is program evaluation. This research function is carried out by the Community Programs Evaluation Centre on the campus of the University of Western Ontario in London.

The work of the Community Programs Evaluation Centre is directed primarily toward assessing the effectiveness and efficiency of treatment, of primary prevention/health promotion, and of Employee Assistance Programs in the community supported or promoted by the Foundation through its regional offices. The main concern is to ensure that the people of Ontario are provided with addiction-related services and programs that are optimally cost-effective. Because relevant evaluation procedures are built into wide-scale programs and local community projects from the beginning, outcomes can be assessed and opportunities identified to initiate necessary improvements along the way.

J.C. La Rocque
Director, Community Services Division

COMMUNITY PROGRAMS EVALUATION
Program Manager: M. Faveri

The aims of Community Programs Evaluation research are as follows:

1. To evaluate the Action Plan of the Addiction Research Foundation;
2. To evaluate the Foundation's work in the employee assistance area;
3. To evaluate education and health promotion programs provided by the Foundation through its Regional Programs Division.

1. Evaluation of Programs Designed to Improve Treatment Systems in Ontario

Since 1979, approximately 40% of the human resources of the Foundation's Community Services Division has been devoted to the implementation of a program called the Action Plan. The long-term goal of the Action Plan is to improve the delivery of services to the people of Ontario experiencing alcohol- and/or drug-related problems by developing a series of specific community-based services, which include assessment/referral services, case management, detoxication, day care, outpatient counselling, and halfway house programs. In December 1985, the Ontario Ministry of Health announced an Addiction Services Policy that advocates the development of a continuum of addiction services in each community in Ontario and is highly consistent with the goals of the Foundation's Action Plan.

To date, research activities relevant to the Action Plan have focused on monitoring its implementation, on evaluating assessment/referral services that have been established, and on monitoring all Ontario addiction treatment services relative to the entire series of specific community-based services advocated by the Foundation.

Service Development. A survey of Foundation staff activities and achievements shows that considerable progress has been made toward establishing frameworks for the development of community-based treatment systems. Also, many new components of such systems have already been established or are being planned. A detailed case study of the treatment system in Kent County showed that it has many features in common with the Foundation's model of treatment services and that the Kent County system reflects very positively on the efforts of local Foundation staff and other local professionals. Of particular significance is the fact that the Kent County system functions satisfactorily without making extensive use of inpatient treatment services.

A monitoring system for assessment/referral services has been established and twelve such services are currently involved in providing data for this system. Included are two newly established assessment/referral services run by the Addiction Research Foundation. These two services are also being carefully evaluated, and it is expected that the results of these evaluations will have wide-ranging implications for other assessment/referral services.

A proposal to evaluate the Foundation's recommended assessment instrument (the ASIST) has recently been developed. Evaluation will involve a survey of users of the ASIST and an experimental comparison of parts of the ASIST with an alternative instrument designed to assess alcohol consumption. Overall this proposal seeks to demonstrate that the ASIST is a valid and useful instrument for identifying the treatment needs of individuals seeking help from assessment/referral services.

Growing concerns about the use of drugs by alcoholics admitted to alcoholism detoxication centres were addressed in a survey of a sample of males admitted to the Foundation's detox centre in Toronto. This was a collaborative project involving staff in the Community Services Division and the Clinical Institute. The results have stimulated interest in further studies of drug use in detox centres and in a review of the mandate of such centres.

Case Management. In the development of community-based treatment systems, the Foundation has stressed coordination and continuity of care. To achieve these ends, much of community development has focused on ensuring that persons entering addictions treatment systems receive systematic assessment and case management.

Case management is a service that provides relapse prevention and ongoing support for the client, as well as liaison with other agencies involved in helping the client. Although case management is a crucial part of addictions treatment (indeed, an important part of mental health treatment programs generally), very little evaluation has been done to determine how case management can be most efficiently and effectively conducted within addictions treatment systems. Evaluation research is currently being conducted to establish a model for defining case management, to describe how case management services are currently implemented in addictions programming across the province, and to evaluate specific kinds of case-management programs. This research should help to develop guidelines for providing case management in the most cost-effective manner while maintaining the flexibility and responsiveness essential in the supportive and liaison role implicit in the provision of case management.

Alcohol and the Elderly. Many elderly people experiencing problems with alcohol or other substances are unwilling to enter addictions treatment programs designed primarily for younger people. To address their needs, an innovative program has been established with a major evaluation component. The evaluation includes the development of valid measures to monitor client progress in the program as well as the collection of detailed documentation of the kinds of services provided by the program. The results of this evaluation will have direct implications for developing suitable treatment programs for elderly substance abusers in the province.

Provincial Survey. Every three years, a survey of addiction-specific programs in Ontario is undertaken in order to monitor changes in the delivery of alcoholism and drug-abuse treatment and to provide up-to-date information for program planning. The last survey was implemented during 1983 and

the results summarized and distributed across the province in 1984–85. Compared to baseline data from 1979–80, the results showed a continued growth in services specializing in the assessment and treatment of addictions. The largest growth was in the number of assessment/referral services and community-based outpatient programs. Hospital-based residential services were comparatively stable. The next update of the survey is currently under way.

Investigators: K. Graham, A. Osborne, B. Rush

2. Evaluation of Employee Assistance Programs

The development and improvement of Employee Assistance Programs (EAPs) for the workforce of Ontario has been a priority of the Foundation for many years. Foundation goal number 6 calls for an increase in "the effectiveness of identification and referral for assistance of individuals in Ontario's workforce whose alcohol- and drug-related problems are interfering with their work performance." The Community Services Division, through the Community Programs Evaluation Centre, is committed to the systematic monitoring and evaluation of EAP methods and practices implemented by field staff throughout the province.

In evaluating the efficiency and effectiveness of EAP work within the division, the focus of research is on three major areas: (a) monitoring and evaluating the interventions within the division in this area through the development of program data-based information systems; (b) describing and evaluating the probabilities of success for people referred to EAPs; and (c) assisting in the evaluation of processes and outcomes of EAPs.

In 1984, a survey of organizations served by Foundation field staff was undertaken to assess the nature and extent of work in the EAP area. At that time, it was found that approximately 10% of Ontario's workforce was being reached through ARF efforts in consultation, training, policy development, and provision of assessment and referral. This represents a 4% increase over the 1983 penetration rate of 6%. The survey also revealed that a wide range of job sectors, including public administration, manufacturing, mines, utilities, and many others, are presently being served by Foundation staff.

Research has been conducted on the characteristics of people who are most likely to remain employed at an organization following referral to the EAP. It was found that people with strong social supports (e.g., married) and who had five or more years' working experience were most likely to be successful in remaining employed at the organization. Additionally, females were more likely than males to remain employed following referral.

Foundation field staff have implemented numerous EAPs throughout Ontario. Some of these programs have incorporated follow-up designs to monitor referral rates and success. Frequently, field staff have conducted awareness surveys in order to assess the degree to which employees are aware of and are willing to utilize EAPs. Our efforts in conjunction with field staff have been directed toward developing useful means of evaluating such EAP issues.

Investigator: S. Macdonald

3. Evaluation of Public Education and Health Promotion Programs

Since the early 1980s increasing attention has been directed toward the prevention/health promotion area by the Community Services Division. In addition to seeking to develop systems designed to help people in need, more focus has been given to promoting healthy lifestyles in general, and specifically with respect to the use of alcohol and drugs. A formal statement of objectives prepared in early 1984 provided focus and direction to staff efforts in this important area.

The goal of the division in public education and health promotion is to increase public knowledge and awareness of the effects of problematic use of alcohol and drugs, and to encourage the adoption of preventive measures through the identification of public health benefits.

With primary focus on three substances — alcohol, cannabis, and tobacco — the division has delineated several areas in which staff are to focus their resources: children and youth; alcohol- and drug-related traffic accidents; public health units; substance-use management policies and regulatory measures; and district health councils, volunteer agencies, concerned citizen groups, and the general public.

In line with this health promotion perspective, in 1984–86 the Evaluation Centre has been involved in a number of significant research endeavors designed to facilitate, evaluate, and improve the division's efforts in many of these specific areas.

The Campus Alcohol Policies and Education project (CAPE) was developed by ARF staff to warn first-year students about problems they may encounter at university with respect to alcohol use, and to prevent problems from arising. As such, it targets a segment of the population usually exempt from health promotion activities. Because of the novel approach of CAPE, it has undergone an extensive evaluation that utilized mail-out surveys to students, personal interviews with students, and reviews of sales data of campus bars. The results of the study, which included a comparison site, have been quite positive and encouraging. Not only has the program achieved penetration throughout the university population (i.e., most students know about the program and its objectives), but students also seem to approve of the messages of the campaign and its general philosophy. In addition, the outcome component of the evaluation has suggested that students have developed more positive attitudes with respect to alcohol use and may even have reduced the frequency and quantity of alcohol use.

Although the Community Services Division devotes a great deal of resources to health promotion in the school system, little systematic information exists about the overall extent of such programming. In order to provide such information, and to provide data on geographic areas where such programming is lacking and/or desired, a survey of all boards of education in the province of Ontario has been undertaken. Directors of education were asked to designate a board employee who could answer detailed information about the extent and type of alcohol/drug and other education that is taking place within their board's schools. Each designated individual will be contacted and given a structured interview over the telephone. This information will

be given to community consultants, who will have knowledge about local resources and needs and who may acquire a needed entry into the system. Future surveys will be able to indicate the extent to which the existing gaps in alcohol and drug education in the province have been filled.

Other evaluation activities are being conducted with segments of the general population. With the increased emphasis on drinking and driving, several programs have been developed that involve roadside checks by the police. Surveys have been planned that will gauge the reactions of the community to the programs and the extent to which the program is visible and seems to be working.

Investigator: L. Gliksman

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